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Proposed Registration Decision PRD2016-23

Pyriofenone

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Overview

Proposed Registration Decision for Pyriofenone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Technical Pyriofenone Fungicide and Pyriofenone 300SC Fungicide, containing the technical grade active ingredient pyriofenone, to control or suppress powdery mildew in cucurbits and certain berry crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Technical Pyriofenone Fungicide and Pyriofenone 300SC Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on Pyriofenone, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on Pyriofenone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Pyriofenone?

Pyriofenone is a fungicide active ingredient with preventative and systemic properties for control or suppression of powdery mildew on various crops.

Health Considerations

Can Approved Uses of Pyriofenone Affect Human Health?

Pyriofenone 300SC Fungicide is unlikely to affect human health when used according to label directions.

Potential exposure to pyriofenone may occur through the diet (food and water) or when handling and applying Pyriofenone 300SC Fungicide. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, pyriofenone and Pyriofenone 300SC Fungicide, were of low acute toxicity by the oral, dermal, and inhalation routes of exposure. They were both non-irritating to the eyes and skin and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of pyriofenone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were abortions and adverse effects noted in the kidneys. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. The risk assessment protects against the effects of pyriofenone by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most pyriofenone relative to body weight, are expected to be exposed to less than 9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyriofenone is not of health concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of pyriofenone is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using pyriofenone on representative commodities of Crop Group 9, Cucurbit Vegetables, and of Crop subgroup 13-07A (Caneberries), Crop subgroup 13-07B (Bushberries), Crop Subgroup 13-07D (Small fruit climbing) and Crop subgroup 13-07G (Low growing berries) are acceptable, in addition to residue trials conducted throughout Europe using pyriofenone on grapes. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Risk in Residential and Other Non-Occupational Environments

Risk to bystanders is not of concern when Pyriofenone 300SC Fungicide is used according to the proposed label directions.

Application is limited to agricultural crops, only when there is low risk of drift to areas of human habitation or activity, such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings. Therefore, bystander exposure is expected to be minimal.

The occupational re-entry worker exposure to treated crops was not of concern and, therefore, any potential exposure to bystanders in a pick-your-own scenario is also not of concern.

Occupational Risks From Handling Pyriofenone 300SC Fungicide

Occupational risks are not of concern when Pyriofenone 300SC Fungicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Pyriofenone 300SC Fungicide, as well as field workers re-entering freshly treated fields, can come in direct contact with pyriofenone residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Pyriofenone 300SC Fungicide must wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves made of any waterproof material. The label, Pyriofenone 300SC Fungicide, also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications, and the expectation of the exposure period for handlers and workers, the risk to these individuals from exposure to pyriofenone are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Pyriofenone Is Introduced Into the Environment?

Pyriofenone is not expected to pose risks of concern to the environment when used according to label directions.

Pyriofenone enters the environment when it is sprayed on cucurbit vegetables, berries and other small fruit plants to protect them against fungi. Once on the leaves, pyriofenone may be distributed throughout the plant.

In the terrestrial environment, pyriofenone residues tend to bind to soil particles and remain in the top soil layers. Pyriofenone can be broken down by microorganisms faster in soils low in oxygen. Pyriofenone is slightly persistent to persistent in soil, and can carry over to the following growing season. Pyriofenone has a slight potential for mobility in some soils and has limited potential to move through the soil to enter groundwater.

Pyriofenone does not react with water and has a limited potential to transform under sunlight. If it enters the aquatic environment, pyriofenone tends to move from the water column to the sediments. Pyriofenone residues tend to bind to sediment particles and can be broken down faster by microorganisms in sediments low in oxygen. Pyriofenone is not expected to accumulate in fish tissues.

Pyriofenone formed only two major degradation products in control laboratory studies. These two products are structurally similar to pyriofenone and tend to be produced at higher concentrations in the absence of oxygen in both the soil and water/sediment systems. Pyriofenone's degradation products are not expected to be of concern to the environment. Residues of pyriofenone are not expected to volatilize to air or accumulate in the tissues of animals.

Overall, when used according to the label directions, pyriofenone is expected to pose a negligible risk to terrestrial invertebrates, birds, mammals, terrestrial and aquatic plants, freshwater invertebrates, fish (freshwater and marine) and amphibians. Pyriofenone may pose a slight risk to freshwater algae and marine invertebrates. In order to minimize the potential risk of pyriofenone to these organisms, precautionary label statements, as well as mitigation measures, are specified on the label of the end-use product (refer to section on Measures to Minimize Risk below). Pyriofenone 300SC Fungicide is not expected to pose risks of concern to the environment when used according to label directions.

Value Considerations

What Is the Value of Pyriofenone 300SC Fungicide?

Pyriofenone 300SC Fungicide contains a new active ingredient, pyriofenone, which will control or suppress powdery mildew in cucurbits and certain berry crops.

Pyriofenone 300SC Fungicide has been identified as a priority by Canadian growers for control of powdery mildew on blackberry and cucumber. There are currently other conventional and non-conventional fungicides registered for control or suppression of powdery mildew on the crops. Nevertheless, the addition of a new active ingredient from a different mode of action group will offer an alternative to the growers to manage powdery mildew, and help address resistance development in susceptible fungi.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Pyriofenone 300SC Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with pyriofenone on the skin, anyone mixing/loading and applying Pyriofenone 300SC Fungicide must wear a long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves made of any waterproof material. In addition, standard label statements to protect against drift during application are on the label.

Environment

Additional label statements under the Environmental Precautions section are required to inform the user that:

- Pyriofenone is persistent and may carry over to the following growing season;
- Pyriofenone is toxic to aquatic organisms; and
- To mitigate potential exposure of aquatic organisms through spray drift, spray buffer zones of 1 metre are required to protect sensitive freshwater and marine aquatic habitats and must be specified on the labels of Pyriofenone 300SC Fungicide.

Next Steps

Before making a final registration decision on Pyriofenone, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

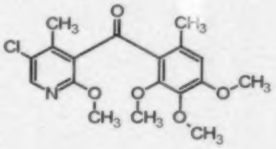
When the PMRA makes its registration decision, it will publish a Registration Decision on Pyriofenone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Pyriofenone

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	pyriofenone
Function	fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(5-chloro-2-methoxy-4-methylpyridin-3-yl)(2,3,4-trimethoxy-6-methylphenyl)methanone
2. Chemical Abstracts Service (CAS)	(5-chloro-2-methoxy-4-methyl-3-pyridinyl)(2,3,4-trimethoxy-6-methylphenyl)methanone
CAS number	688046-61-9
Molecular formula	$C_{18}H_{20}ClNO_5$
Molecular weight	365.81
Structural formula	 O CH3 CH3 Cl N O CH3 O CH3 O CH3 O CH3
Purity of the active ingredient	98.3%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product – Pyriofenone Technical

Property	Result
Colour and physical state	White crystalline powder
Odour	no odour
Melting range	93-95°C
Boiling point or range	Not applicable since the product is a solid
Density at 20°C	1.36 g/mL
Vapour pressure at 25°C	1.9×10^{-6} Pa

Henry's law constant at 20°C	4.40×10^{-9} atm.m^3/mole $1/H = 5.56 \times 10^6$
Ultraviolet (UV)-visible spectrum	Medium* — λ_{max} (nm) — absorbance Purified water — 298 — 0.534 0.1M aq. HCl — 298 — 0.559 0.1M aq. NaOH — 297 — 0.540 * Each medium also contained 4% (v/v) methanol
Solubility in water at 20°C	1.56 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) n-heptane — 8.8 xylene — > 250 1,2-dichloroethane — > 250 acetone — > 250 methanol — 22.3 n-octanol — 16.0 ethyl acetate — > 250
n-Octanol-water partition coefficient (K_{OW})	$\log_{10}K_{ow} = 3.2$
Dissociation constant (pK_a)	No dissociation was observed in the environmental range of pH 4-10
Stability (temperature, metal)	Stable in contact with aluminum, aluminum acetate, iron, iron acetate, zinc, and zinc acetate, and when stored at 54°C for 14 days in the dark.

End-Use Product—Pyriofenone 300SC Fungicide

Property	Result
Colour	Beige
Odour	No odour detected
Physical state	Viscous liquid
Formulation type	Suspension (SU)
Guarantee	300 g/L
Container material and description	Plastic
Density	Relative density = 1.08 at 20°C
pH of 1% dispersion in water	6.0 at 20°C
Oxidizing or reducing action	The product does not have oxidizing properties.
Storage stability	The product is stable for 2 weeks at 54°C in HDPE containers.

Corrosion characteristics	No corrosion to the HDPE container was observed when the product was stored for 2 weeks at 54°C.
Explodability	Based on the assessment of chemical structure of the active ingredient and the formulants, the product will not have explosive properties.

1.3 Directions for Use

Pyriofenone 300SC Fungicide is intended for control and suppression of powdery mildew pathogens on various crops. Pyriofenone 300SC Fungicide is to be applied as a foliar treatment in a preventative program. Three to four applications at 0.3-0.366 L/ha (90-110 g a.i/ha) are recommended on all crops with a 7-10 or 14 days interval.

1.4 Mode of Action

Pyriofenone proposed mode/target site of action, as defined by the Fungicide Resistance Action Committee (FRAC), is actin disruption, Fungicide Group U8. The confirmation of the mode/target site of action has not been established by FRAC.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

A high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS; Method ISK 0341/074208 in plant matrices) method was developed and proposed for data generation and enforcement purposes in commodities of plant origin. This method fulfilled the requirements with regards to specificity, accuracy and precision at the respective limit of quantitation of the method. Acceptable recoveries (70–120%) were obtained in plant matrices. The method was successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled grapes, wheat and tomatoes analyzed with the enforcement method. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for pyriofenone was conducted. The database consists of the full array of toxicity studies currently required for health hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is acceptable. The database is considered adequate to define the majority of toxic effects that may result from exposure to pyriofenone.

Metabolism and toxicokinetics were investigated using radiolabelled pyriofenone (^{14}C-(phenyl)-IKF-309 and ^{14}C-(pyridyl)-IKF-309) in single low and high dose, as well as repeated low dose oral gavage (^{14}C-(phenyl)-IKF-309) studies in the rat. Absorption was rapid with peak plasma concentrations (T_{max}) reached within 4-24 h of dosing. Elimination half lives ($t_{½}$) ranged from 13 to 46 h. Absorption (% of administered dose) was higher at the low dose level than at the high dose level. The maximum plasma concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were similar for both sexes regardless of position of radiolabel. Excretion was similar and rapid for both radiolabels. Elimination via expired air was very low. Following single low- and high-dose administration, the main route of elimination was fecal via the bile, while urinary excretion played a minor role. Radioactivity levels in the tissues were low, and generally higher in males than females. Overall tissue accumulation after single oral doses was low. Radioactivity in tissues after repeated dosing was generally 2- to 10-fold higher than after single oral doses. The highest levels of radioactivity were detected, in ascending order, in the GI tract, liver, kidneys, and plasma. In females, radioactivity was also detectable in abdominal fat after administration of a high-dose. Concentrations in tissues declined rapidly over time.

Metabolism of pyriofenone was limited and unchanged pyriofenone was the major component excreted in the faeces. Other metabolites were excreted as an unstable conjugate of the metabolite 2MDPM and as glucuronide conjugates of 3HDPM and 4HDPM.

In the rat, the acute toxicity of pyriofenone was low by the oral, dermal, and inhalation routes of exposure. Pyriofenone was non-irritating to the eyes and skin of the rabbit. It was not a potential skin sensitizer based on the results of the local lymph node assay in the mouse.

Assessment of acute toxicity studies with Pyriofenone 300SC Fungicide showed that it was of low acute toxicity by the oral, dermal, and inhalation routes of exposure in rats. The product was not an eye or skin irritant in rabbits and was not considered to be a skin sensitizer based on the results of sensitization testing using the Buehler's test protocol.

In repeated-dose gavage/dietary toxicity studies in mice, rats, and dogs, the liver, kidneys, and the cecum were the main target organs. At high doses, pyriofenone induced increased weights of the liver, kidneys, and cecum, as well as hepatocellular hypertrophy, and hyaline deposition in the kidneys.

No systemic toxicity or localized skin effects occurred in rats following daily dermal application of pyriofenone for 28 days.

Pyriofenone was tested for potential genotoxic activity in a battery of in vitro and in vivo assays. Based on the uniformly negative results of these studies, pyriofenone was not considered genotoxic.

In long-term dietary toxicity studies in rats and mice, histopathological alterations were similar to those observed in shorter term studies. Although more effects were observed with extended duration of exposure, the effects were generally not severe. Increased weights of the liver, kidneys, and cecum were observed. The liver showed hepatocellular hypertrophy and necrosis. The kidneys exhibited tubular basophilia, scarring, and chronic nephropathy.

There was no evidence of oncogenic potential of pyriofenone in rats and mice.

A dietary reproductive toxicity study in rats did not demonstrate reproductive toxicity. A high dose level caused parental toxicity similar to that observed in other short- and long-term toxicity studies.

Developmental toxicity studies were conducted in rats and rabbits via oral gavage. The high dose induced maternal toxicity in both species. In the rabbit study, two abortions occurred on gestation day 18 in high-dose dams that displayed decreases in body weight and food consumption prior to aborting. There was no other developmental toxicity observed.

There were no gross or histopathological changes in either the central or peripheral nervous system following either acute gavage or subchronic dietary exposure to pyriofenone in the rat. No treatment-related behavioural changes were observed.

Immunotoxicity studies in female rats and mice demonstrated that pyriofenone did not affect the weights of the spleen and thymus. There were no effects on spleen cellularity or the numbers of spleen plaque forming cells.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Information on the reporting of incidents can be found in the PMRA website. Pyriofenone is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient pyriofenone have been reported to the PMRA and the applicant did not submit any additional data.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contained the standard complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in the rat.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of the young animals compared to parental animals in the reproductive and developmental toxicity studies. In the rat reproductive toxicity study, there were no effects on reproduction or on the offspring. No developmental toxicity was demonstrated in the rat developmental toxicity study. In the rabbit developmental toxicity study, two abortions occurred in dams receiving pyriofenone at maternally toxic doses.

Overall, the database is adequate for determining the sensitivity of the young. The abortions were considered serious endpoints although concern was tempered by the presence of maternal toxicity. Therefore the *Pest Control Products Act* factor was reduced to 3-fold when using the rabbit developmental toxicity study to establish the point of departure for risk assessment. The *Pest Control Products Act* factor was reduced to 1-fold for all other scenarios.

3.2 Acute Reference Dose (ARfD)

No effects attributable to a single dose were observed, thus an ARfD is not required for pyriofenone.

3.3 Acceptable Daily Intake (ADI) for all populations

To estimate risk from repeat dietary exposure, the 2-year dietary toxicity study in the rat with a NOAEL of 9.1 mg/kg bw/d was selected. At the LOAEL of 46.5 mg/kg bw/d, chronic nephropathy was observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The ADI proposed is calculated according to the following formula:

$$\mathrm{ADI} = \frac{\mathrm{NOAEL}}{\mathrm{CAF}} = \frac{9.1\,\mathrm{mg/kg\,bw/d}}{100} = 0.09\,\mathrm{mg/kg\,bw/d}$$

This ADI provides a margin of 1111 to the NOAEL for abortion in the rabbit developmental toxicity study.

Cancer Risk Assessment

There was no evidence of carcinogenicity and therefore a cancer risk assessment was not necessary.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to pyriofenone is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation route.

Short- and Intermediate-term Dermal and Inhalation Exposure

For short- and intermediate-term exposure via the dermal and inhalation routes, the rabbit oral development toxicity study was selected for risk assessment because of the severity of the end-point (abortions). A NOAEL of 100 mg/kg bw/d was established for both maternal and developmental toxicity. At the LOAEL of 300 mg/kg bw/d two dams showed significant reduction in food intake and reduced body-weight gain; the dams aborted their fetuses subsequently. The target margin of exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection to the fetus that may be exposed via its mother. The concerns outlined in the *Pest Control Products Act* Hazard Characterization Section are also relevant to the worker population and therefore an additional 3-fold factor was applied to this endpoint to protect the unborn children of women of child-bearing age. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

An *in vitro* human dermal penetration study was submitted in support of the registration of pyriofenone. An *in vitro* dermal absorption study cannot be used alone to establish a dermal absorption value. As such, in the absence of sufficient and appropriate chemical specific dermal absorption studies, the default dermal absorption factor of 100% was maintained for pyriofenone for risk assessment purposes.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Foliar Uses of Pyriofenone

Pyriofenone 300SC Fungicide can be applied to cucurbits (Crop Group 9), strawberries, grapes, caneberries (Crop subgroup 13-07A), gooseberries, and Saskatoon berries.

3.4.2.1.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to pyriofenone during mixing, loading and application. Exposure to workers mixing, loading and applying pyriofenone is expected to occur primarily by the dermal and inhalation routes. Farmers are expected to be exposed for short-term duration, and custom applicators are expected to be exposed for intermediate-term duration. Exposure estimates were derived for mixers/loaders/applicators applying pyriofenone to the cucurbit crop group (Crop Group 9) and strawberries using groundboom equipment. Exposure estimates were also derived for mixer/loaders/applicators applying pyriofenone to grapes, caneberries, gooseberries, and Saskatoon berries using airblast equipment. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt and long pants, shoes, socks, and chemical-resistant gloves.

As chemical-specific data for assessing human exposures during pesticide handling activities were not submitted, dermal and inhalation exposure estimates for workers were generated using the Pesticide Handlers Exposure Database (PHED), version 1.1 (for groundboom application) and the Agricultural Handlers Exposure Task Force (AHETF) data (for airblast application).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints to obtain the margin of exposure (MOE). Dermal and inhalation MOEs were combined, since the dermal and inhalation endpoints are based on the same toxicological effects. Calculated MOEs are above the target MOE of 300 for all chemical handler scenarios, and therefore, was not of concern.

Table 3.4.2.1.1 Mixer/Loader/Applicator Exposure Estimates and MOEs

Crop	Job task	PHED unit exposure (µg/kg a.i. handled)			Rate (kg a.i./ha)	ATPD (ha/day)[1]	Daily exposure (mg/kg bw/day)[2]			MOE[3]
		Derm	Inhal	Comb			Derm	Inhal	Comb	
PPE: Single layer (and chemical-resistant gloves when mixing and loading, and applying by airblast)										
Groundboom application										
Cucurbits (CG9) and strawberries	M/L/A	84.12	2.56	86.68	0.110	26	0.00301	9.15×10^{-5}	0.00310	32270
Airblast application										
Grapes, caneberries (CSG 13-07A) Gooseberries, Saskatoon Berries	M/L/A	3820.44	10.68	3831.12	0.110	20	0.105	2.94×10^{-4}	0.105	949

Derm = dermal, Inhal = inhalation, Comb = combined, ATPD = area treated per day, MOE = margin of exposure, M/L/A = Mixer/loader/applicator

[1] Default Area Treated per day values

[2] Daily exposure = (PHED/AHETF unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[3] Dermal/Inhalation: based on NOAEL= 100 mg/kg bw/day, target MOE = 300

3.4.2.1.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers entering areas treated with pyriofenone while performing activities such as scouting, irrigating, hand harvesting, thinning, tying, and training. The duration of exposure is considered to be short- to intermediate-term for all uses. The primary route of exposure for workers re-entering treated areas would be through the dermal route. Inhalation exposure is not considered to be a significant route of exposure for workers entering treated areas compared to the dermal route, since pyriofenone is relatively non-volatile (1.9×10^{-9} kPa at 25°C) and as such, an inhalation risk assessment was not required.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients (TCs). Activity TCs are based on United States Environmental Protection Agency Policy 3.1 and Agricultural Re-entry Task Force (ARTF) data.

Two chemical-specific dislodgeable foliar residue (DFR) studies were submitted to estimate dislodgeable foliar residues and their dissipation on foliage of summer squash plants and grapes. For summer squash, the study was conducted at three test sites in North Carolina, North Dakota, and California. For grapes, the study was also conducted at three test sites in Pennsylvania, California, and Washington. For both studies, four applications of IKF-309 300SC, a suspension concentrate containing a nominal 300 g a.i./L pyriofenone, were made to summer squash at the rate of 0.087 to 0.092 kg a.i./ha/application and to grapes at the rate of 0.087 to 0.091 kg a.i./ha/application. The re-treatment intervals were 6-8 days. Applications were made using ground application equipment (groundboom sprayer for summer squash and airblast for grapes). There were no surfactants/adjuvants included in the spray mixtures, except for the North Carolina site for summer squash. Samples were taken just prior to the first and last applications, and 1 hour after the last application, 8 hours after the last application, and at 1, 2-3, 3-4, 5-6, 9-10, 13-14, 21, 27-28, and 34-35 days after the final application for each site. Field fortification sample recoveries were 79.7 – 99.0%, except for high fortification samples in North Dakota for squash DFR (67.7%), high fortification samples in Pennsylvania for grape DFR (54.1%), and high fortification samples in Washington for grape DFR (63.1%). Dislodgeable foliar residue values were corrected for field recovery when the overall average for a fortification level was <95%. For all sites and residues, DFR residues were closest to the low fortification sample level; therefore, the low recoveries for some of the high fortification sample level did not affect confidence in the study data. First-order dissipation kinetics were assumed to generate dissipation curves for pyriofenone.

The results from the DFR studies were compared in each site, and the climate of study sites and representative Canadian sites were also compared. As such, the following values from the DFR studies were used in the risk assessment:

- Predicted peak residue values of 0.2107 µg/cm^2 (from the summer squash study) and 0.3192 µg/cm^2 (from the grape study) for Day 0 DFR after the final application

  - These residue values were chosen from the California site (for summer squash) and from the Washington site (for grapes) because they were the highest predicted peak residue values across all the sites from each study.

- 13% (from the summer squash study) and 4.9% (from the grape study) dissipation per day
  - These dissipation rates were chosen from the California site (for summer squash) and the Washington site (for grapes) because the R-squared values of the dissipation curves was higher than 0.85 and these dissipation rates were the lowest across all sites for each study.

Given that the summer squash DFR study was conducted with a groundboom sprayer, the DFR values from the study were used for DFR calculations of cucurbit vegetables (Crop Group 9) treated by groundboom. Similarly, given that the grape DFR study was conducted with an airblast sprayer, the DFR values from the study were used for DFR calculations for grapes, caneberries (Crop subgroup 13-07A), gooseberries, and Saskatoon berries. Since strawberries have a different crop morphology from grapes, and are typically treated with groundboom application equipment, DFR calculations for strawberries were made using default DFR values (25% of the application rate deposited per application for Day 0 DFR, and 10% dissipation per day). The value of 10% dissipation for strawberries is considered a reasonable estimate of dissipation for groundboom application to strawberries when compared to the dissipation values indicated by the submitted DFR studies (13-44% for summer squash and 4.9-8.2% for grapes). Post-application exposure was calculated with Day 0 DFR after the last application for all activities.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE. The calculated MOEs are all above the target MOE of 300, except for the re-entry activities of cane turning and girdling in table grapes. The restricted entry interval (REI) of 12 hours and preharvest intervals (PHIs) are adequate to protect re-entry workers for all crops except grapes. For grapes, an REI of 16 days is required for cane turning and girdling in grapes. The REI of 12 hours for all other re-entry activities and the PHI are adequate to protect re-entry workers in grapes.

Table 3.4.2.1.2 Post-application Re-entry Worker Exposure Estimates and MOEs

Crops (CG = crop group)	# of apps	Rate (g a.i./ha)	Post-application activity	DFR (µg/cm^2)[1]	TC (cm^2/hr)[6]	Exposure (mg/kg bw/day)[7]	Calculated MOE	REI required
Cucurbits (CG9)	4	90	Hand-set irrigation	0.2107[1]	1750	0.0369	2712	12 hrs
	3	110		0.2575[2]		0.0451	2219	12 hrs
Caneberries (CSG 13-07A), Gooseberries, Saskatoon Berries	4	90	Hand-set irrigation	0.3192[3]	1750	0.0559	1790	12 hrs
	3	110		0.3901[4]		0.0683	1465	12 hrs
Strawberries	4	90	Hand harvest	0.4087[5]	1100	0.0450	2224	12 hrs

Crops (CG = crop group)	# of apps	Rate (g a.i./ha)	Post-application activity	DFR ($\mu g/cm^2$)[1]	TC (cm^2/hr)[6]	Exposure (mg/kg bw/day)[7]	Calculated MOE	REI required
	3	110		0.4694[5]		0.0516	1937	12 hrs
Grapes	4	90	Tying, training, hand harvesting, leaf pulling	0.3192[3]	8500	0.271	369	12 hrs
			Hand-set irrigation		1750	0.0559	1790	12 hrs
	3	110	Girdling, turning	0.3901[4]	19300	0.753	133	16 days
			Tying, training, hand harvesting, leaf pulling		8500	0.332	302	12 hrs
			Hand-set irrigation		1750	0.0683	1465	12 hrs

[1] Based on predicted peak residue on Day 0 after final application and 13% dissipation per day from summer squash DFR study

[2] With the DFR study conducted at 90 g a.i./ha, the residue level of 0.2107 $\mu g/cm^2$ was extrapolated linearly up to the higher proposed application rate of 110 g a.i./ha using the equation: [(Use Pattern Rate/Study Application Rate) * DFR on Day 0], giving an initial DFR residue value of 0.2575 $\mu g/cm^2$

[3] Based on predicted peak residue on Day 0 after final application and 4.9% dissipation per day from grape DFR study

[4] With the DFR study conducted at 90 g a.i./ha, the residue level of 0.3192 $\mu g/cm^2$ was extrapolated linearly up to the higher proposed application rate of 110 g a.i./ha using the equation: [(Use Pattern Rate/Study Application Rate) * DFR on Day 0], giving an initial DFR residue value of 0.3901 $\mu g/cm^2$

[5] Strawberry DFR calculated using default DFR values of 25% of application rate deposited per application and 10% dissipation per day

[6] Transfer coefficients from ARTF Database

[7] Exposure = (Peak DFR × TC × 8 hr/day) / (80 kg bw × 1000 $\mu g/mg$)

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is mainly limited to agricultural crops, only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is pyriofenone. The HPLC-MS/MS enforcement analytical method is valid for the quantification of pyriofenone residues in crop matrices. The residues of pyriofenone are stable when stored in a freezer at -10 to -20°C for 18 months in grapes, and wheat grain, and straw and for 9 months in summer squash. Pyriofenone residues concentrated in the processed commodity raisins (2.9x). There are no animal feed items associated with the use of pyriofenone, and quantifiable residues are not expected to occur in livestock matrices. Supervised residue trials conducted throughout Canada the United States and the European Union using end-use products containing pyriofenone at exaggerated and/ or approved rates in or on grapes, strawberries, blackberries, highbush blueberries, kiwis, cucumbers, cantaloupe and summer squash are sufficient to support the proposed maximum residue limits.

3.5.1.1 Exposure From Drinking Water

3.5.1.1.2 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) for the combined residues of pyriofenone and its major transformation products in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. EECs of pyriofenone in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are average concentrations in the top one metre of the water table. EECs of pyriofenone in surface water were calculated using the SWCC model, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated for a small reservoir.

Six of the pyriofenone transformation products share the phenyl-hydroxyl-pyridyl nucleus with the parent molecule. To be conservative, the environmental half-lives used in the drinking water concentration assessment models were calculated from the combined residues of the active ingredient and the transformation products 3HDHP, 2MDPM, 4MDPM, 3HDPM, 4HDPM, and PTBA.

The results of the Level 1 drinking water assessment, conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario are presented in Table 3.5.1.1.2, below. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate.

Table 3.5.1.1.2 Level 1 Estimated Environmental Concentrations (Parent Equivalent) of the Combined Pyriofenone Residues in Potential Drinking Water Sources

Use Pattern	**Groundwater (µg a.i./L)**		**Surface Water (µg a.i./L)**	
			Reservoir	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
4 × 90 g a.i./ha @ 14 days	0.081	0.081	14.1	1.17

1 90th percentile of daily average concentrations
2 90th percentile of 365 day moving average concentrations
3 90th percentile of the peak concentrations from each year

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[4] 90th percentile of yearly average concentrations

3.5.2 Dietary Risk Assessment

The chronic non-cancer dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis for pyriofenone: 100% crop treated, default processing factors, and residues of pyriofenone in crops at maximum residue limit values. The basic chronic dietary exposure from all supported pyriofenone food uses (alone) and importation of treated commodities for the total population, including infants and children, and all representative population subgroups is less than 9% of the acceptable daily intake (ADI).

Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to pyriofenone from food and drinking water is <2% (7.3×10^{-4} mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 8.0% (7.2×10^{-3} mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for pyriofenone consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.4 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Crop Group 9, Cucurbit Vegetables	0.3
Crop Subgroup 13-07B: Bushberries	1.5
Crop Subgroup 13-07D: Small fruits vine climbing	1.5
Crop Subgroup 13-07A: Caneberries	0.9
Crop Subgroup 13-07G: Low growing berries	0.5

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodologies, field trial data, and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Pyriofenone has low water solubility and exists in its neutral form in the environmentally relevant pH range. It binds strongly and has very low mobility in soils. Leaching potential for pyriofenone and its major transformation products is considered minimal; however, given their persistence in soil, the possibility that they may eventually reach groundwater cannot be ruled out.

The method of Gustafson (1989) may also be used to estimate the leaching potential of pesticides. The GUS score calculated from half-lives and adsorption coefficients in different soils classifies pyriofenone as a non-leacher or borderline leacher.

All of the characterized pyriofenone transformation products (refer to Table 7, Appendix 1), with the exception of CO_2, are structurally similar to the parent molecule. As no ecotoxicity or environmental fate data were submitted to characterise these transformation products, they were assumed to be of equal toxicity to the parent, and estimated environmental concentrations were calculated from the combined residues of the active ingredient and the transformation products 3HDHP, 2MDPM, 4MDPM, 3HDPM, 4HDPM, and PTBA.

In the terrestrial environment, pyriofenone is slightly persistent to persistent. A minimal amount of mineralization was observed in the laboratory studies (up to 29% applied radioactivity (AR) as CO_2). Chemical processes including volatilization, phototransformation and hydrolysis are not expected to contribute to overall dissipation of pyriofenone. In terrestrial field studies, significant amounts of pyriofenone were found at the beginning of the following growing season, indicating that pyriofenone can carryover.

Tables in section 1.2 present the physical and chemical properties that influence the fate of pyriofenone in the environment. In Appendix 1, Table 8, presents a summary of the rates of pyriofenone transformation from soil laboratory degradation studies; Table 9, the transformation products from soil laboratory degradation studies, and Table 10 the soil-binding properties of pyriofenone from laboratory studies. Table 11 presents the levels of pyriofenone approximately one year after the last application in field studies; and Table 12, the maximum pyriofenone concentration in the various soil depths in field studies.

Although the use pattern of Pyriofenone 300SC Fungicide does not include direct application to water, it can enter the aquatic environment through spray drift and runoff from the application field. Pyriofenone has low water solubility and, in the aquatic environment, it partitions from the water to the sediment layers. Pyriofenone does not hydrolyze but is non- persistent to slightly persistent in aerobic and anaerobic water and sediment systems due to microbial transformation and adsorption.

In both terrestrial and aquatic studies, unextracted residues accounted for up to 85% AR. An aerobic biodegradation test conducted with sterilized soil suggested that microorganisms play in important role in the adsorption of pyriofenone residues. In this study, the degradation of pyriofenone in sterilized soil was not significant during the 30 day incubation, and the levels of non-extracted residues remained very low, (max. 1.4% AR) even though the soil was rich in organic carbon (3.5% OC). In contrast, after the same incubation period in non-sterile soil, the levels of pyriofenone decreased to 77.8% and 82.0% AR, and the levels of unextracted residues reached 7.8% and 14.1% AR for the ^{14}C-(phenyl)- and ^{14}C-(pyridyl)- labels.

In Appendix 1, Table 13 presents a summary of the rates of pyriofenone transformation from water-sediment laboratory degradation studies, and Table 14, the transformation products from water-sediment laboratory degradation studies.

The two major transformation products observed in soil and water-sediment studies, 3HDPM and 2MDPM, were produced at levels above 10% applied radioactivity only under anaerobic conditions, and were not monitored in the field studies.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse ecological effects. This integration is achieved by comparing exposure concentrations (for example the EECs) with concentrations at which adverse effects occur (for example, toxicity endpoints such as LC_{50}, LD_{50}, NOEC or NOEL). For characterizing acute risk, acute toxicity values (for example, LC_{50}, LD_{50}, and EC_{50}) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (i.e., feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the NOEC or NOEL is used and an uncertainty factor is not applied.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC = 1 for most species, 0.4 for pollinators and 2 for beneficial arthropods (acute screening tests for predatory mite and parasitoid wasp)). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

The environmental risk of pyriofenone and its related end-use product to non-target organisms was assessed based upon the maximum annual application rate of 360 g a.i./ha to field vegetables of Crop Group 9 and berries (4 × 90 g a.i./ha, with a 7-day interval) or following the highest single application rate of 110 g a.i./ha.

In Appendix 1, Table 15 presents a summary of EEC values used for the risk assessment; Table 16, modelled sediment pore water concentrations used to estimate exposure of sediment-dwelling organisms; and Table 17, the expected environmental concentration in vegetation and insects used as food by birds and small wild mammals.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of pyriofenone and its end-use product formulation Pyriofenone 300SC Fungicide was undertaken for terrestrial organisms based on available toxicity data. A summary of toxicity data is presented in Table 18 of Appendix 1. Results of the accompanying risk assessment for terrestrial organisms are presented in Tables 19 to 23 of Appendix 1.

At the screening level, EECs from lumped pyriofenone residues (combined residues of pyriofenone and its major transformation products) for direct on-field application were considered for soil dwelling organisms, beneficial arthropods, pollinators, birds, mammals and terrestrial vascular plants. As the screening level risk quotients for terrestrial organisms were all below the level of concern, a refined risk assessment was not necessary.

Earthworms

One acute toxicity study was conducted to assess the toxicity of pyriofenone to earthworms (*Eisenia fetida*). Significant mortality was not observed in worms exposed to pyriofenone technical for 14 days and the LC_{50} value was greater than the highest test concentrations (i.e., >979.8 mg a.i./kg dw soil. The resulting screening level risk quotient is below the level of concern indicating a negligible risk to earthworms.

Foliar dwelling beneficial arthropods

To assess the toxicity to foliar-dwelling arthropods, two acute laboratory studies were conducted with Pyriofenone 300SC Fungicide.

Screening level: The screening level risk assessment for foliar-dwelling organisms exposed to pyriofenone considers the acute toxicity obtained from laboratory experiments using glass plates. Two species were exposed to the Pyriofenone 300SC Fungicide formulation: the parasitoid wasp (*Aphidius rhopalosiphi*), and the predatory mite (*Typhlodromus pyri*). The 48h acute LR_{50} for parasitoid wasp was >1000 g a.i./ha and the 14-day acute LR_{50} for the predatory mite was >1035 g a.i./ha. At the highest foliar application rate of 4 × 90 g a.i./ha with 7 days interval, the screening level EEC for direct over spray is 201g a.i./ha, and the corresponding RQ < 0.2, well below the LOC of 2, indicating a negligible risk for beneficial arthropods.

Honeybees

The toxicity of technical pyriofenone to adult honeybees was assessed in a 48h acute oral and 48h contact exposure study, and a 10 day chronic exposure study. The risk to honeybee larvae was assessed in a single exposure 72h acute test.

Contact exposure: Honey bees can be exposed to pyriofenone from direct application or contact with treated plant material. Pyriofenone is proposed for a maximum annual foliar application rate of four applications of 90 g a.i./ha at an interval of 7 days in Canada, however the single application rate is used because foraging bees are expected to only be exposed to residues resulting from a single application. The maximum single application rate for Pyriofenone 300SC Fungicide is 110 g a.i./ha. In order to compare the application rate to the acute contact toxicity endpoint derived in laboratory studies (µg a.i./bee), a conversion from kg a.i./ha to µg a.i./bee is required. The proposed upper-bound residue value for estimating exposure to honey bees is based on the maximum residue value reported by Koch and Weisser 1997 (2.4 µg a.i./bee per 1 kg a.i./ha). The estimated residues per bee following a single application of 110 g a.i./ha is 0.264 µg a.i./bee. A risk quotient (RQ) was calculated by dividing this value by the 48h contact LD_{50} value of >100 µg a.i./bee for the technical active ingredient. The LOC for the Tier 1 acute exposure is 0.4. The calculated RQ is <0.01 which does not exceed the LOC; therefore foraging worker bees are not expected to be at risk from direct contact exposure of pyriofenone residues following single foliar applications at 110 g a.i./ha.

Oral exposure: The acute oral exposure estimate for adult bees is calculated by multiplying the single application rate (110 g a.i./ha) by 29 µg a.i./bee per kg a.i./ha for adult bees, and by 12 µg a.i./bee per kg a.i./ha for larval bees. This conversion is based on nectar consumption rates (0.292 g/day for forager bees, and 0.124 g/day for bee larvae) primarily derived from Rortais et al. (2005) and Crailsheim et al (1992 and 1993) and concentrations in pollen and nectar (98 µg a.i./g) estimated from the T-Rex model. Following the conversion, the estimated oral exposure based on an application rate of 110 g a.i./ha is 3.14 µg a.i./bee/day for adult bee and 1.34 µg a.i./bee/day for bee larvae. The acute RQ is calculated by dividing this value by the 48h oral LD_{50} value of >100 µg a.i./bee (identical for both adult and larvae).

The calculated acute RQs are <0.03 and <0.01 for adult and larval bees, respectively, which does not exceed the LOC of 0.4. Therefore pyriofenone in nectar and pollen following foliar applications is not expected to pose a risk to adult or larval bees.

In the chronic risk study to adult bees, mortalities did not follow a clear dose-response relationship, with means varying between 10% (in the second highest treatment group) and 38% (in the highest treatment group). A NOEL of 27 µg a.i./bee/day was determined by comparison against the solvent control and the associated RQ = 0.12, indicating negligible risk to pollinators.

Risk Assessment Conclusions

Acute toxicity testing with young adult bees and bee larvae indicates that pyriofenone is practically non-toxic to honeybees on an acute contact and oral exposure basis (LD_{50} value of >100 µg a.i./bee). The risk quotients for acute exposure were below the level of concern of 0.4 for both adult and larval honeybees. While variable, the results from of a ten day exposure test with worker honeybees suggest that pyriofenone is unlikely to pose a chronic risk to honeybees.

Birds and mammals

Pyriofenone is practically non-toxic to Northern bobwhite quail (*Colinus virginianus*), mallard duck (*Anas platyrhynchos*) and canary (*Serinus canaria*) on both an acute oral and acute dietary exposure basis (bobwhite quail and canary oral LD_{50} values >1958 and >2000 mg a.i./kg bw; and bobwhite quail and mallard duck dietary LD_{50} values respectively >980 mg a.i./kg bw/d, and > 1290 mg a.i./kg bw/d). Chronic exposure to pyriofenone resulted in no treatment-related adverse effects on reproductive parameters or on the parental generation for bobwhite quail or mallard duck up to the highest test concentration, with resulting NOELs of 96 mg a.i./kg bw/d and 120 mg a.i./kg bw/d, respectively.

Based on the available data, pyriofenone is practically non-toxic to small mammals (rats) on an acute oral basis with the most sensitive LD_{50} of >2000 mg a.i./kg bw. In a rat two-generation reproduction study, pyriofenone had no adverse effects on the study parameters and the resulting NOAEL was 334 mg a.i./kg bw/d.

Birds and mammals may be exposed to pyriofenone following the ingestion of plant materials and insects sprayed with pyriofenone during foliar application. The screening level risk assessment for Pyriofenone 300SC Fungicide is conducted for direct on-field exposure, assuming exposure occurs entirely through the consumption of food sources contaminated with pyriofenone at the maximum nomogram residue levels, the most conservative scenario. Concentrations of pyriofenone on different food guilds (EDE) are calculated based on the highest rate for foliar application (i.e., 4 × 90 g a.i./ha) with a 7-day interval and a foliar half-life of 10 days.

The screening level risk assessment shows that for the worst case exposure scenario RQs for acute adverse effects and reproductive effects are below the LOC of 1 for all sizes of birds and mammals (RQs ≤ 0.17). Therefore, pyriofenone poses a negligible risk for birds and mammals foraging in treated fields up to the highest seasonal application rate of 360 g a.i./ha.

Non-target terrestrial vascular plants

The toxic effects of pyriofenone on vegetative vigour and seedling emergence of terrestrial vascular plants were tested at the maximum nominal application rate of 360 g a.i./ha using the Pyriofenone 300SC Fungicide formulation. Inhibition of survival, shoot length and shoot dry weight did not exceed 25% in any of the six dicotyledonous and four monocotyledonous species tested in either the seedling emergence or vegetative vigor studies. A screening level assessment was conducted for the Pyriofenone 300SC Fungicide formulation using the on-field EECs based on the maximum application rates of 4 × 90 g a.i./ha and a mean measured ER_{25} of >360 g a.i./ha for both seedling emergence and vegetative vigour. Risk quotient values for both exposures are below the LOC of 1, suggesting that there is a negligible risk to non-target terrestrial plants.

4.2.2 Risks to Aquatic Organisms

Aquatic organisms can be exposed to pyriofenone as a result of spray drift and runoff. To assess the potential for adverse effects, screening level EECs in the aquatic environment were calculated based on a direct application of 4 × 90 g a.i./ha at a 7 day interval and an aquatic whole-system representative half-life of 25.5 days at 20°C (i.e. the longest available aerobic aquatic T_R from lumped residues) to a 15-cm deep water body representing a seasonal pond suitable for amphibians and an 80-cm deep water body representing a permanent pond. Pyriofenone was assumed to be instantaneously and completely mixed within the water body. The resulting EECs were 0.185 mg a.i./L for a water body of 15 cm in depth and 0.035 mg a.i./L for a water body of 80 cm in depth.

A risk assessment of technical pyriofenone and Pyriofenone 300SC Fungicide was undertaken for freshwater and marine aquatic organisms based on available toxicity data to algae (acute), aquatic plants (acute), invertebrates (acute and chronic), fish (acute and chronic) and amphibians (based on surrogate data for freshwater fish). A summary of toxicity data for pyriofenone is presented in Table 18, Appendix 1. Results of the accompanying risk assessment for aquatic organisms are presented in Tables 24 and 25.

Algae and plants

For freshwater species: Acute toxicity studies to freshwater green algae (*Pseudokirchneriella subcapitata*), blue-green algae (*Anabaena flos-aquae*) and the diatom *Navicula pelliculosa* were performed with pyriofenone technical. Statistically significant ($p<0.05$) effects on yield, growth rate and area under the curve were noted at low concentrations.

In the *A. flos-aquae* study, cell density was the most sensitive endpoint and followed a dose-response among the five lowest treatment groups (5.7, 14, 36, 91 and 224 µg a.i./L); however, the magnitude of inhibition (percent compared to the control) decreased with increasing pyriofenone concentration at the two highest treatment groups (565 and 1413 µg a.i./L). Because a sound EC_{50} value based on yield could not be determined from the complete dataset, a more conservative EC_{50} value based on yield of 0.062 mg a.i./L was determined from the linear section of the data, omitting the two higher treatment groups.

The EC_{50} for *P. subcapitata* and *N. pelliculosa* were 0.340 mg a.i./L and 1.669 mg a.i./L. Screening level RQs for the green algae and the diatom fall below the LOC of 1, however, a screening level of RQ of 1.1 was calculated for the blue-green algae endpoint, indicating that the risk to freshwater algae needs to be refined.

The acute toxicity to aquatic vascular plant duckweed (*Lemna gibba*) was determined for pyriofenone in a static-renewal system. No statistically significant ($p<0.05$) inhibition on the growth rate or biomass of *L. gibba* was observed up to the highest test concentration. The EC_{50} was determined to be > 1.574 mg a.i./L. A screening level RQ of < 0.04 was below the LOC of 1, indicating that pyriofenone poses a negligible risk to freshwater plants.

For estuarine/marine species: Acute toxicity to the saltwater diatom (*Skeletonema costutum*) was determined for pyriofenone. Inhibition was less than 50% in all measurement parameters. Area under the growth curve was the most sensitive as inhibition reached a maximum of 37% in the 1.349 mg a.i./L (mean-measured) treatment group. An EC_{50} of 2428 µg a.i./L, which is greater than the limit of aqueous solubility of pyriofenone, was calculated from the calculated area under the growth curve. As the estimated EC_{50} is greater than the reported limit of aqueous solubility, it is considered as >1.349 mg a.i./L. A screening level RQ of < 0.05 was below the LOC of 1, indicating that pyriofenone poses a negligible risk to marine algae.

Aquatic invertebrates

For freshwater species: Both acute and chronic tests on aquatic invertebrates, including *Daphnia magna* (water dwelling) and *chironomus* (sediment dwelling) were performed for technical pyriofenone. An acute study with *Daphnia magna* was also conducted with Pyriofenone 300SC Fungicide.

Daphnia magna: In the acute 48h toxicity test on *D. magna*, no mortalities were observed in any of the treatment groups up to the mean measured pyriofenone concentration of 1.55 mg a.i./L. The resulting EC_{50} was > 1.55 mg a.i./L and the resulting RQ was <0.04. With Pyriofenone 300SC Fungicide, higher active ingredient concentrations were achieved. The EC_{50} with the formulated active ingredient was 36.8 mg a.i./L and its associated RQ was <0.01. When *D. magna* was exposed to technical pyriofenone on a chronic basis, reproduction was significantly affected in the 0.188 mg a.i./L group, and the $NOEC_{(reproduction)}$ = 0.089 mg a.i./L. The screening level RQ of 0.4 was below the LOC of 1, indicating that technical pyriofenone and its formulated product pose a negligible risk to *D. magna* on an acute or chronic basis.

Chironomus: In a 28 day spiked overlying water emergence study with technical pyriofenone, no mortality or sublethal effects were observed in the midge (*Chironomus riparius*) exposed to concentrations up to the highest concentration. The NOAEC, expressed as pore water and overlying water concentration was, respectively, ≥ 92.5 µg a.i./L, and ≥ 833 µg a.i./L. The RQs calculated from the overlying water concentration and from modelled pore water concentrations (Table 16) fall below the LOC of 1 (RQ < 0.04) indicating that pyriofenone is expected to pose a negligible risk to sediment-dwelling freshwater organisms.

Estuarine/marine species: The Eastern oyster (*Crassostrea virginica*), mysid shrimp (*Americamysis bahia*) and the marine amphipod *Leptocheirus plumulosus* were used to test the acute toxicity of pyriofenone to marine invertebrates. The mysid shrimp was also used to test pyriofenone's chronic toxicity to marine invertebrates.

Eastern oysters exposed to pyriofenone under continuous flow-through conditions showed no mortalities or sub-lethal effects other than inhibition of shell growth. An EC_{50} of 1.10 mg a.i./L and an RQ of 0.06 was calculated based on shell deposition results.

For the mysid shrimp *A. bahia*, exposed under flow-through conditions, the calculated LC_{50} of 0.79 resulted in an RQ of 0.09, below the LOC of 1.

For the marine amphipod *L. plumulosus*, the LC_{50} based on overlying water and pore water concentrations were 0.353 and 0.491 mg a.i./L, respectively. The respective RQs of 0.19 and 0.01 were below the level of concern.

The chronic toxicity of pyriofenone to the saltwater mysid (*Americamysis bahia*) was studied under flow-through conditions. A NOEC of 0.033 mg a.i./L and an associated RQ of 1.04 was calculated based on treatment-related effects on reproduction endpoints (number of offspring per surviving female).

As all of the calculated acute risk quotients for the available marine invertebrate studies fall below the level of concern, pyriofenone is expected to pose a negligible risk to these organisms when used at a concentration of up to 360 g a.i./ha. Because the screening level risk quotient associated with the saltwater mysid reproduction endpoint is equal to the level of concern, the chronic risk to marine invertebrates was further explored below, in a Tier I risk assessment.

Fish

For freshwater species: Acute toxicity of pyriofenone to fish was determined for the rainbow trout (*Oncorhynchus mykiss*), representing cold-water species; and fathead minnow (*Pimephales promelas*) and the common carp (*Cyprinus carpio*) representing warm water species. The chronic toxicity of pyriofenone to fish was determined in an Early-Life-Stage (ELS) test with the fathead minnow.

Following 96h of exposure to technical pyriofenone, there were no mortalities observed at any test concentration in any of the fish species. In all cases, the acute LC_{50} was greater than the highest test concentration, which was limited by pyriofenone's low solubility in water. Higher pyriofenone concentrations were achieved in the study conducted with Pyriofenone 300SC Fungicide. In this study, no toxic effects were noted up to a concentration of 4.85 mg a.i./L, and the 96h LC_{50} was 13.7 mg a.i./L. In the chronic (ELS) test with fathead minnow, hatchability, average days to hatch, rate of developmental abnormalities, and survival rate after hatching showed no significant differences between the exposure groups and the solvent control. However, statistically significant decreases in body weight and total body length were observed for the group exposed to a measured concentration of 0.904 mg a.i./L compared to the solvent control group. The LOEC and NOEC values were 0.904 and 0.403 mg a.i./L, respectively.

Acute and chronic RQs for all species were below the LOC of 1.0 (RQs < 1.0), indicating a negligible risk to freshwater fish.

For estuarine/marine species: Acute and chronic toxicity of pyriofenone to marine/estuarine fish was determined with saltwater sheepshead minnow (*Cyprinodon variegatus*). In the acute test on sheepshead minnows, pyriofenone did not cause mortality or sublethal effects following 96 hours of exposure. The LC_{50} was >1.27 mg a.i./L, the highest concentration tested, and the associated RQ was <0.3. In the chronic ELS study with sheepshead minnow, growth was the most sensitive biological endpoint measured in this study. Sheepshead minnows exposed to technical pyriofenone at concentrations ≥0.57 mg a.i./L had significant reductions in total length, wet weight and dry weight in comparison to the control. Consequently, the NOEC, based on growth, was 0.293 mg a.i./L and the corresponding RQ was 0.1, well below the LOC of 1.

Marine fish are therefore not expected to be at risk from pyriofenone up to the highest use rate of 360 g a.i./ha per season.

Amphibians

The risk to amphibians was determined using acute and chronic toxicity data from the most sensitive fish endpoints. The acute LC_{50} from the study conducted with fathead minnow, and the NOEC from the chronic ELS endpoint from the marine sheepshead minnow were used as surrogate amphibian endpoints. The risk quotient for acute exposure for amphibians in 15 cm water was < 1.6. As the screening level of concern is slightly exceeded, risk to amphibians is further discussed under the Tier I risk assessment.

Tier I Refinement – Aquatic Organisms

The potential for acute risk to algae and amphibians, and chronic risk to marine invertebrates was further characterized since the screening level risk quotients for these organisms slightly exceeded the levels of concern. In this section, the risk is characterized on the basis of more realistic exposure scenarios that are likely to occur under operational field conditions. This includes any refinements to the determination of the exposure characterization or toxicity value.

The acute risk to amphibians was based on an acute toxicity endpoint with a surrogate species (fathead minnow) that did not result in any mortality or observed sublethal toxicity at a concentration near the active ingredient's limit of solubility in water. Because no signs of toxicity were observed in this study, the LC_{50} was above the highest tested concentration, and a NOEC based on mortality and behaviour was determined to be equal to 1.15 mg a.i./L. Using this endpoint, the direct overspray RQ falls below the level of concern (RQ=0.16), which indicates that there will be a negligible risk to amphibians on an acute basis resulting from applications up to 360 g a.i./ha.

As the screening risk quotients for freshwater blue-green algae and marine invertebrates were slightly over the level of concern (RQs = 1.1 and 1.04, respectively), refined environmental concentrations for adjacent off-field aquatic habitats were calculated based on input from spray drift. A separate assessment for runoff, however, was not conducted given the relatively small exceedance of the LOC.

Exposure through spray drift

The refined EECs for spray drift were calculated for field sprayer applications at a rate up to 360 g a.i./ha (i.e., 4 × 90 g a.i./ha at a minimum 7 day interval, Appendix 1 Table 25). Assuming a 6% drift deposition factor for this type of application to water bodies 1 m downwind of the site of application, the refined EEC values calculated in a 80 cm deep water body is 0.0021 mg a.i./L. As some of the labeled listed crops could also be sprayed with an airblast sprayer, the off-field risk was also calculated assuming a 74% drift deposition (the estimate for early airblast). The off-field EECs for airblast in a 15 and 80 cm deep water body are 0.1365 mg a.i./L and 0.0256 mg a.i./L, respectively.

The off-field RQs for algae and marine invertebrates associated with spray drift 1 m from the treated area fall below the level of concern, indicating that foliar application up to 360 g a.i./ha will pose a negligible risk to these organisms in waterbodies downwind of the treatment area (Table 25, Appendix 1).

5.0 Value

5.1 Consideration of Benefits

Pyriofenone 300SC Fungicide has been identified as a priority by Canadian growers for control of powdery mildew on blackberry and cucumber. There are currently other conventional (FRAC Groups 3, 7, 11, 13, M) and non-conventional (*Bacillus subtillis*) fungicides registered for control or suppression of powdery mildew on these crops, refer to Appendix I, Table 26, for a summary of the active ingredients currently registered for control or suppression of listed diseases. However, the addition of a new active ingredient from a different mode of action group will offer an alternative to the growers to manage powdery mildew, and help prevent resistance development in susceptible fungi. Pyriofenone 300SC Fungicide can be used in conjunction with current management practices, including integrated pest management, for control or suppression of powdery mildew on the labelled crops.

5.2 Effectiveness Against Pests

Powdery mildew on Cucurbit Vegetables (Crop Group 9)
The level of efficacy of Pyriofenone 300SC Fungicide was demonstrated in 16 trials under various disease pressures, application intervals, rates, and crops. Pyriofenone 300SC Fungicide provided control of *Podosphaera xanthii* or *Erysiphe cichoracearum* in 11 trials out of 16 trials. The level of control obtained with Pyriofenone 300SC Fungicide was comparable to the commercial standards in all trials. Pyriofenone 300SC Fungicide is more efficacious in terms of severity than incidence of powdery mildew.

Pyriofenone 300SC Fungicide seems to perform better under low to moderate disease pressure. The use of the higher rate and shorter application interval had a positive impact on the level of efficacy, especially under higher disease pressure.

Powdery mildew on Grapes

The level of efficacy of Pyriofenone 300SC Fungicide was demonstrated in 10 trials under various disease pressures, application intervals and rates. Pyriofenone 300SC Fungicide applied at the label rate and interval provided control, in terms of severity, of *Erysiphe necator* on the leaves and the fruit cluster. As observed in the cucurbit vegetable results, Pyriofenone 300SC Fungicide was more effective at reducing disease severity, than disease incidence, of powdery mildew. The level of control obtained with Pyriofenone 300SC Fungicide was comparable to the commercial standards in all trials.

Powdery mildew on Strawberries

The level of efficacy of Pyriofenone 300SC Fungicide was demonstrated in eight trials under various disease pressures, intervals and rates. In all trials, Pyriofenone 300SC Fungicide applied at the tested rate and interval provided suppression of the disease in terms of severity and incidence of *Podosphaera aphanis*. The highest level of efficacy in terms of incidence (~82% control) and severity (~82% control) was obtained in one trial under low disease incidence and high disease severity. However, as the incidence and severity increased toward the end of the trial, the level of control decreased to 63% control of incidence and severity with the highest label rate. Pyriofenone 300SC Fungicide increased marketable yield by an average of 9 %.

Powdery mildew on Saskatoon berries

The efficacy of Pyriofenone 300SC Fungicide against *Podosphaera clandestina* was demonstrated in three trials on cherries. The different pyriofenone treatments provided suppression of powdery mildew by reducing the severity by 25% to 66%. These results can be extrapolated to Saskatoon berries since both crops are affected by the same powdery mildew pathogen. In addition, crop biology and architecture are similar.

Powdery mildew on Caneberries & Goose berries

The claim of suppression can be extrapolated from strawberries (*Podosphaera aphanis*, originally *Sphaerotheca macularis*) to caneberries and goose berries since these crops are affected by the same powdery mildew pathogen.

5.3 Non-Safety Adverse Effects

There was no phytotoxicity observed in any of the efficacy trials. A dedicated phytotoxicity trial on grapes demonstrated very low and acceptable phytotoxicity at the label rates.

5.4 Supported Uses

The claims of control of powdery mildew on cucurbits (Crop Group 9) and grapes are supported as proposed. The claims of powdery mildew on strawberries, caneberries, goose berries and Saskatoon berries are supported as suppression. Refer to Appendix 1, Table 27 for details of the supported uses.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the Canadian Environmental Protection Act].

During the review process, pyriofenone and its major transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria (Table 6.1-1). The PMRA has reached the following conclusions:

- Pyriofenone does not meet all Track 1 criteria, and is not considered a Track 1 substance (Table 6.1.1).

- Pyriofenone does not form any major transformation products that meet all Track 1 criteria. Based on their structural similarity with the parent active ingredient and the log K_{ow} of the parent, the two major transformation products are expected to be below the Track 1 criterion for bioaccumulation.

Table 6.1.1 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
Toxic or toxic equivalent according to the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]	Soil	Half-life ≥ 182 days	Yes: Half-life 49-155 days; longest

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

			T_R 210 d
	Water/Sediment system	Half-life ≥ 182 days (water) ≥ 365 days (sediment)	No: Half-life 5-14.2 days; longest $T_R = 14.2$ days
	Air	Half-life ≥ 2 days or evidence of long range transport	N/A: Non-volatile. Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.9×10^{-6} Pa) and Henry's Law Constant (4.40×10^{-9} atm.m^3/mole; $1/H = 5.56 \times 10^6$).
Bioaccumulation[4]	Log $K_{OW} \geq 5$		No: Log $K_{OW} = 3.2$
	BCF ≥ 5000		No: 160x for whole fish , 165x for other parts and 435x for viscera
	BAF ≥ 5000		N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criteria may be refined if required (that is, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

> The end-use product, Pyriofenone 300SC Fungicide, contains the preservative 1,2-benzisothiazoline-3-one which contains low levels of dioxins and furans. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP.

Based on the formulating process used, other formulants and impurities of human health or environmental concern are not expected to be present in this product or carried through from the technical grade active ingredient.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for pyriofenone is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. In the rabbit developmental toxicity study, abortions were preceded by signs of maternal toxicity. Pyriofenone was not neurotoxic after single and repeat-dose administration. In short- and long-term studies in laboratory animals, toxicity of pyriofenone was manifested mainly by the effects on the liver, kidneys, and cecum.

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[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[8] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

[9] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

There was no evidence of oncogenic potential of pyriofenone in rats and mice. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in plants (grapes, tomatoes and wheat) is adequately understood. The residue definition for enforcement purposes is pyriofenone. The use of pyriofenone on grapes in the European Union, on Crop Group 13-07 Berry and Small Fruits except Crop Subgroup 13-07C Large Shrub/Tree Berry in the United States, and the proposed use of pyriofenone on Crop Group 9 Cucurbit Vegetables and on grapes, strawberries, caneberries, gooseberries and Saskatoon berries in Canada, do not constitute a risk of concern for chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of pyriofenone.

Commodity	Recommended MRL (ppm)
Crop Group 9, Cucurbit Vegetables	0.3
Crop Subgroup 13-07B: Bushberries	1.5
Crop Subgroup 13-07D: Small fruits vine climbing	1.5
Crop Subgroup 13-07A: Caneberries	0.9
Crop Subgroup 13-07G: Low growing berries	0.5

7.2 Environmental Risk

Pyriofenone is slightly persistent to persistent in the terrestrial environment and non-persistent to slightly persistent in the aquatic environment. Pyriofenone residues in soil may carry over to the following growing season. Pyriofenone is relatively immobile in soil and has a limited potential to leach to groundwater. It may enter aquatic environments through spray drift or surface runoff. In aquatic environments, pyriofenone will move from the water to the sediments. Pyriofenone is not expected to pose a risk to non-target terrestrial organisms, but it may present a slight risk to freshwater algae and marine invertebrates. Therefore, one meter buffer zones to reduce exposure of freshwater and marine habitats are required to mitigate the risk to these sensitive organisms.

Toxic substance management policy considerations

Pyriofenone and its major soil and aquatic transformation products do not meet all the TSMP criteria for a Track 1 substance.

7.3 Value

The value information submitted to register Pyriofenone 300SC Fungicide for control or suppression of powdery mildew is adequate to demonstrate value, including efficacy for use on the labelled crops and diseases.

Priorities ranging from low to high have been identified by the Canadian growers for control of powdery mildew on blackberry and cucumber, but with different active ingredients. There are currently other conventional (FRAC Groups 3, 7, 11, 13, M) and non-conventional (*Bacillus subtillis*) fungicides registered for control or suppression of powdery mildew on the label crops. However, the addition of a new active ingredient from a different mode of action group will offer an alternative to the growers to manage powdery mildew, and help address resistance development in susceptible fungi.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Technical Pyriofenone Fungicide and Pyriofenone 300SC Fungicide, containing the technical grade active ingredient pyriofenone, to control or suppress powdery mildew in cucurbits and certain berry crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	female
↑	increase
↓	decrease
≥	equal to or greater than
>	greater than
≤	equal to or lower than
µg	microgram
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
AL	alanine transaminase
ALT	alanine aminotransferase
ALS	acetolactate synthase
AP	alkaline phosphatase
APTT	activated partial thromboplastin time
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate transaminase
atm	atmosphere
ATPD	area treated per day
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
bw	body weight
bwg	body-weight gain
C_{max}	maximum concentration
FcmCAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
CG	crop group
cm	centimetres
d	day(s)
DAFA	days after the first application
DALA	days after last application
DF	dry flowable
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the time required to observe a 75% decline in concentration)

DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EEC	estimated environmental concentration
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
ELS	Early-Life-Stage
ER_{25}	effective rate for 25% of the population
FC	food consumption
FRD	Food and Drugs Act
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GI	gastrointestinal tract
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
HPLC-MS/MS	High Performance Liquid Chromatography – tandem Mass Spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
kPa	kiloPascal
kg	kilogram
K_d	soil-water partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
m	metre
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit

MS	mass spectrometry
m/z	mass-to-charge ratio of an ion
NAFTA	North American Free Trade Agreement
N/A	not applicable
ND	not detected
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
nm	nanometre
OC	organic carbon content
Pa	Pascals
PBI	plantback interval
PFC	plaque forming cell
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PYO	pick your own
RAC	raw agricultural commodity
RD	residue definition
REI	restricted-entry interval
RTI	Retreatment interval (s)
RQ	risk quotient
RSD	relative standard deviation
SC	soluble concentrate
STMR	supervised trial mean residue
STMdR	supervised trial median residue
SU	suspension
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	transfer coefficient
TLC	thin layer chromatography
T_{max}	time to maximum concentration
T_R	representative half-life
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference PMRA #
Plant	ISK 0341/074208 Enforcement method	Active	HPLC-MS/MS	0.01 ppm Grapes Wheat grain Wheat straw	1933879, 2010555, 2054711, 2376235
Soil	N/A	Active	HPLC-MS/MS	0.001 mg/kg	2376240, 2376243
Surface water	N/A	Active	HPLC-MS/MS	0.05 µg/L	2376247, 2407105
Drinking water	N/A	Active	HPLC-MS/MS	0.05 µg/L	2376247, 2407105

Table 2 Toxicity Profile of Technical Pyriofenone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type /Animal/PMRA #	Study Results
Metabolism/Toxicokinetic, oral (gavage, single dose and repeat dosing) Rat, Wistar ^{14}C-(phenyl)-IKF-309 and ^{14}C-(pyridyl)-IKF-309 (5 and 200 mg/kg bw, single dose) ^{14}C-(phenyl)-IKF-309 (5 mg/kg bw/d, repeated dosing for 15 days) PMRA# 1933874	**Absorption:** After oral administration of ^{14}C-(phenyl)-IKF-309 or ^{14}C-(pyridyl)-IKF-309, absorption of the administered dose (AD) was higher at the low dose level (76-89% AD) than the high dose level (36-53% AD). The bile was an important route of excretion. Absorption was rapid and the peak plasma concentrations (T_{max}) were reached within 4-24 h and the terminal half lives $T_{½}$ ranged from 13 to 46 h. There were no major sex or radiolabel differences in the maximum concentration (C_{max}). The time taken to reach C_{max} (T_{max}) was similar for both sexes. **Tissue distribution:** Radioactivity levels in the tissues were low. Tissue radioactivity was generally higher in the males than the females. Overall tissue accumulation after single oral doses was low with only a small proportion (<1% dose) of the dose retained in tissues at 120 h. Radioactivity in tissues after repeated dosing was generally in the range of 2-10 fold higher than after single oral doses. The highest levels of radioactivity were detected, in ascending order, in the GI tract, liver, kidneys, and plasma. In the females, radioactivity was also detectable in abdominal fat after a high-dose administration. Concentrations in tissues declined rapidly over time.

	Metabolism: Metabolism of IKF-309 was limited and the unchanged IKF-309 was the major component excreted in the faeces. Other metabolites were excreted as an unstable conjugate of 2MDPM and as glucuronide conjugates of 3HDPM and 4HDPM. **Excretion:** Following single low- and high-dose administration or a repeat low-dose administration, the main route of elimination was fecal via the bile (73-91% AD after single oral doses; 99-103% AD after 14 daily doses), while urinary excretion (6-20% AD after single oral doses; 12-13% AD after 14 daily doses) played a minor role. There were no substantial differences in pharmacokinetics of IKF-309 that was labelled at the phenyl (^{14}C-(phenyl)-IKF-309) or the pyridyl (^{14}C-(pyridyl)-IKF-309) positions.
Acute oral Rat, Crl:CD SD PMRA# 1933846	LD_{50} ♀ >2000 mg/kg bw Clinical signs: abnormal body position 3-5 h post-dosing in 2♀ females Low toxicity
Acute dermal Rat, CD PMRA# 2376213	LD_{50} >2000 mg/kg bw Clinical signs: very slight erythema; scabbing ↓ bwg (♀) Low toxicity
Acute inhalation Rat, Sprague Dawley PMRA# 2376215	LC_{50} >5.18 mg/L Clinical signs: clear nasal discharge Low toxicity
Eye irritation Rabbit, New Zealand White PMRA# 2376218	MAS = 0.43/110 Non-irritating
Skin irritation Rabbit, New Zealand White PMRA# 2376222	MAS = 0/8 Non-irritating
Skin sensitization (LLNA) Mouse PMRA# 2376224	Not a skin sensitizer
90-Day dietary Mouse, Crl:CD1 PMRA# 1933847	NOAEL = 7000 ppm (♂ = 1318, ♀ = 1504 mg/kg bw/d), HDT Liver effects (not considered adverse)
90-Day dietary Rat, Fischer PMRA# 1933848	NOAEL = 1000 ppm (♂ = 61, ♀ = 69 mg/kg bw/d) LOAEL = 2500 ppm (♂ = 150, ♀ = 171 mg/kg bw/d) effects included ↑ wts of liver, kidneys, and cecum, ↓ ALT, AST (♂); ↑ liver and cecal wts, prolonged APTT (♀)

90-Day dietary Dog, Beagle PMRA# 1933849	NOAEL = 3000 ppm (90 mg/kg bw/d) LOAEL ♂ = 25000 ppm (776 mg/kg bw/d) based on ↓ bw, ↑ AP & liver effect (↑ wt, centrilobular hepatocyte hypertrophy) ♀ = 15000 ppm (475 mg/kg bw/d) based on ↑ AP & liver effects (↑ wt, centrilobular hepatocyte hypertrophy)
1-Year dietary Rat, Fischer PMRA# 1933850	NOAEL = 1000 ppm (♂= 43, ♀ = 54 mg/kg bw/d) LOAEL = 5000 ppm (♂= 226, ♀ = 275 mg/kg bw/d) based on haematology, clinical chemistry, urinalysis, distended cecum; liver effects (↑ wt, centrilobular hepatocyte hypertrophy), kidney effects (↑ wt, basophilic tubules) (♂); soiled fur; ↓ bw, ↑ liver wt, kidney (↑ wt, hyaline droplets) (♀)
1-Year dietary Dog, Beagle PMRA# 1933858	NOAEL = 500 ppm (14 mg/kg bw/d); LOAEL = 3000 ppm (84 mg/kg bw/d) Based on ↑ AP & ↓ bwg
28-Day dermal Rat, Sprague Dawley PMRA# 2376227	NOAEL = 1000 mg/kg bw/d (HDT)
78-week dietary oncogenicity Mouse, Crl:CD-1 PMRA# 1933852	NOAEL ♂ = 600 ppm (78 mg/kg bw/d), ♀ = 1000 ppm (167 mg/kg bw/d) LOAEL ♂ = 1800 ppm (237 mg/kg bw/d) based on effects on liver (↑ wt, centrilobular hypertrophy, hepatocyte necrosis) and kidney (tubular basophila, scarring, cysts) ♀ = 3000 ppm (487 mg/kg bw/d) based on ↓ bw & bwg No evidence of carcinogenicity
2-Year dietary / oncogenicity Rat, Fischer PMRA# 1933854	NOAEL ♂ = 1000 ppm (36 mg/kg bw/d), ♀ = 200 ppm (9 mg/kg bw/d) LOAEL ♂ = 5000 ppm (197 mg/kg bw/d) based on ↓ bw, soiled fur, effects on liver (centrilobular hypertrophy, fatty change, necrosis), kidneys (↑ wt), & cecum (↑ wt,, distended cecum) ♀ = 1000 ppm (46 mg/kg bw/d) based on chronic nephropathy No evidence of carcinogenicity
2-Generation dietary reproductive Rat, Wistar PMRA# 1933862	Parental systemic toxicity: NOAEL = 1000 ppm (♂ = 64, ♀ = 67 mg/kg bw/d) LOAEL = 5000 ppm (♂ = 334, ♀ = 336 mg/kg bw/d) based on alteration of haematological parameters; distended large intestine, liver and kidney pathology, thyroid hypertrophy Reproductive toxicity: NOAEL = 5000 ppm (♂ = 334, ♀ = 336 mg/kg bw/d), HDT Offspring toxicity: NOAEL = 1000 ppm (♂ = 64, ♀ = 67 mg/kg bw/d) LOAEL = 5000 ppm (♂ = 334, ♀ = 336 mg/kg bw/d) based on ↓ absolute & relative spleen wts
Developmental, oral gavage Rat, Wistar	Maternal toxicity: NOAEL = 300 mg/kg bw/d LOAEL = 1000 mg/kg bw/d based on ↓ food intake; ↑ cecal and liver wt

PMRA# 1933867	Developmental toxicity: NOAEL = 1000 mg/kg bw/d, HDT Low incidence of malformations at maternally toxic dose No evidence of sensitivity of the young.
Developmental, oral gavage Rabbit, Japanese White PMRA# 1933869	Maternal toxicity: NOAEL = 100 mg/kg bw/d LOAEL = 300 mg/kg bw/d based on 2 abortions & ↓ food intake Developmental toxicity: NOAEL = 100 mg/kg bw/d; LOAEL = 300 mg/kg bw/day based on 2 abortions No evidence of sensitivity of the young.
Bacterial reverse mutation assay (Ames test) PMRA# 1933870	Cytotoxicity: nil Precipitation: 1500 & 5000 µg/plate Negative
In vitro mammalian cell gene mutation (mouse lymphoma L5178Y cells) PMRA# 1933871	Cytotoxicity: nil Precipitation: ≥636 µg/plate for 3h exposure; nil for 24h exposure Negative
In vitro chromosome aberration in Chinese hamster lung cells PMRA# 1933872	Cytotoxicity: 70 µg/mL 3 h exposure with S9 Negative
In vivo mouse micronucleus assay NMRI mice (bone marrow) PMRA# 2331423	No mortality or clinical signs Negative
Acute neurotoxicity, oral gavage Rat, Crl:CD PMRA 1933864	NOAEL = 2000 mg/kg bw, HDT No evidence of neurotoxicity
90-Day dietary neurotoxicity Rat, Crl:CD PMRA# 1933865	NOAEL: Systemic toxicity: ♂ = 1000 ppm (62 mg/kg bw/d), ♀ = 5000 ppm (378 mg/kg bw/d) LOAEL: Systemic toxicity: ♂ = 5000 ppm (310 mg/kg bw/d) based on ↓ bwg ♀ = 15000 ppm (1147 mg/kg bw/d) based on ↓ bwg Not neurotoxic
4-Week dietary immunotoxicity Mouse, Crl:CD1 ♀ PMRA# 1933860	Mortality: nil No effects on clinical signs, bw, food or water consumption, wt of spleen or thymus, gross pathology, PFC, spleen cellularity
4-Week dietary	Mortality: nil

immunotoxicity Rat, Sprague Dawley ♀ PMRA# 1933859	20000: ↓ bwg No effects on clinical signs, wt of spleen or thymus, gross pathology, PFC, spleen cellularity

Table 3 Toxicity Profile of Pyriofenone 300SC Fungicide

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study	Study findings
Acute, oral Rat, CD PMRA# 2376488	LD_{50} ♀ >2000 mg/kg bw Low toxicity
Acute, dermal Rat, CD PMRA# 2376490	LD_{50} >2000 mg/kg bw Clinical signs: very slight erythema d 2-6 Low toxicity
Acute, inhalation Rat, Sprague Dawley PMRA# 2376491	LC_{50} >2.78 mg/L Low toxicity
Eye irritation Rabbit, New Zealand White PMRA# 2376493	MAS = 0.2/110 Non-irritating
Skin irritation Rabbit, New Zealand White PMRA# 2376495	MAS = 0/8 Non-irritating
Skin sensitization (Buehler) Guinea pig PMRA# 2376497	Not a skin sensitizer

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Pyriofenone

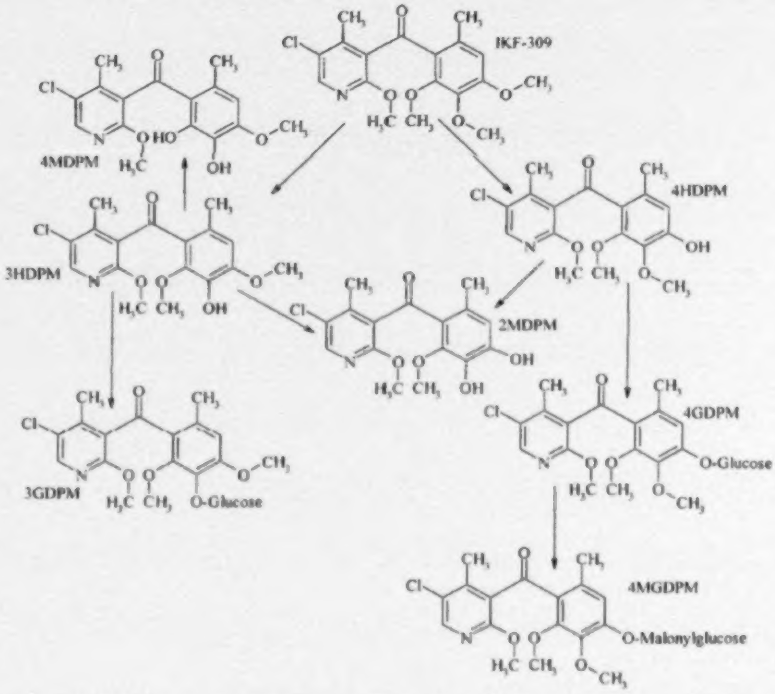
Exposure Scenario	Study	Point of Departure and Endpoint	CAF^1 or Target MOE
Acute dietary	No acute toxicity end-point identified, ARfD not required		
Repeated dietary	2-year rat dietary	NOAEL = 9 mg/kg bw/d Chronic nephropathy	100

	ADI = 0.09 mg/kg bw/d		
Short- & intermediate-term dermal and inhalation exposure	Rabbit developmental	NOAEL = 100 mg/kg bw/d 2 abortions at 300 mg/kg bw/d	300
[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments			

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN GRAPE			**PMRA #1933877, 2054710**	
Radiolabel Position	[Phenyl-U-^{14}C] and [2,6-pyridyl-^{14}C]			
Test Site	Grape vines (6 years old) grown in test plots in California			
Treatment	Broadcast foliar spray applications at BBCH 77, 79 and 85			
Rate	3 × 100 g a.i./ha for a total rate of 300 g a.i./ha			
End-use product	30% suspension concentrate			
Preharvest interval	29 days			
Matrix	**PHI (days)**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**	
		TRR (ppm)	**TRR (ppm)**	
Grape	29	0.103	0.107	
Foliage	29	2.75	3.70	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**
Grape	Pyriofenone	Pyriofenone	3GDPM, 4GDPM, 3HDPM, 4HDPM, 2MDPM, 4MDPM	3GDPM, 4GDPM, 3HDPM, 4HDPM, 2MDPM
Foliage	Pyriofenone	Pyriofenone	3GDPM, 4GDPM, 3HDPM, 4HDPM, 2MDPM, 4MDPM, 4MGDPM	3GDPM, 4GDPM, 3HDPM, 4HDPM, 2MDPM, 4MGDPM

Proposed Metabolic Scheme in Grapes:

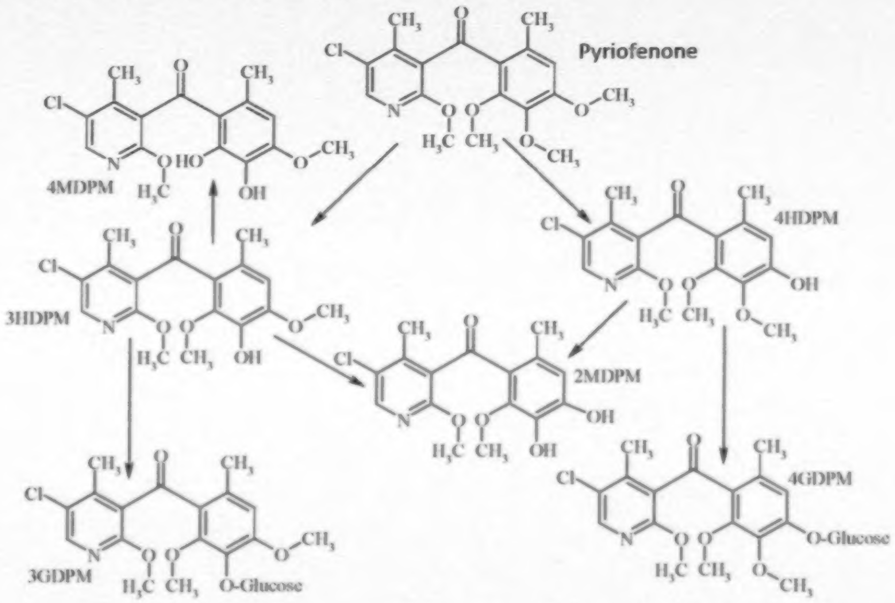


Metabolism of pyriofenone in grape is proposed to result from hydrolysis of the phenyl ring methoxy groups followed by conjugation with naturally occurring sugars.

NATURE OF THE RESIDUE IN WHEAT			**PMRA #2376231, 2418187**
Radiolabel Position	[Phenyl-U-^{14}C] and [2,6-pyridyl-^{14}C]		
Test Site	Winter wheat grown in containers located outdoors in a fenced enclosure.		
Treatment	Two foliar spray applications at BBCH growth stage 31 (first node detectable) and 71 (grain water ripe).		
Total Rate	2 × 100 g a.i./ha for a total rate of 200 g a.i./ha		
Formulation	30% suspension concentrate		
Preharvest interval	Forage - 7 days after the first application (DAFA) at BBCH 32 Hay - six days after the second (last) application (early harvest, 6 DALA) at BBCH 73-75 Straw, grain and chaff - 40 days after the last application (DALA) at BBCH 90-91		
Matrix	**PHI**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**
		TRR (ppm)	**TRR (ppm)**
Forage	7 DAFA	1.69	1.86
Hay	6 DALA	1.21	0.828
Straw	40 DALA	1.23	0.877
Grain	40 DALA	0.059	0.042
Chaff	40 DALA	3.90	2.05

Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**
Forage	Pyriofenone	Pyriofenone	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM
Hay	Pyriofenone	Pyriofenone	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM
Straw	Pyriofenone	Pyriofenone 4HDPM	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM	3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM
Grain	Pyriofenone	Pyriofenone	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM
Chaff	Pyriofenone	Pyriofenone	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM	4HDPM, 3HDPM 3GDPM, 4GDPM, 2MDPM, 4MDPM

Proposed Metabolic Scheme in Wheat:



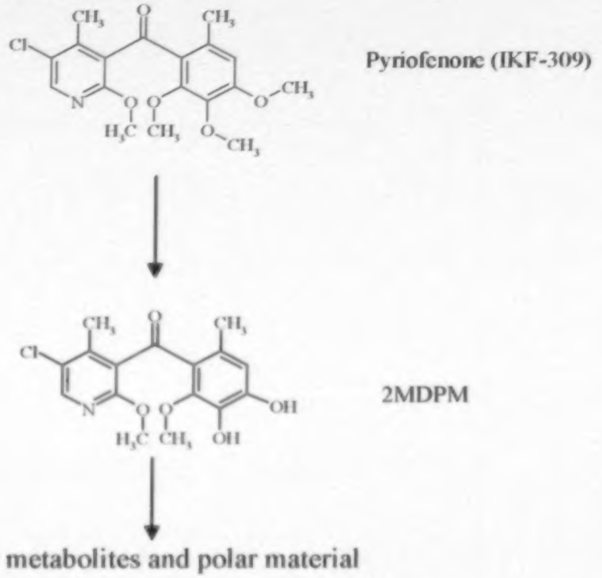
Metabolism of pyriofenone in wheat is proposed to result from hydrolysis of the phenyl ring methoxy groups followed by conjugation with naturally occurring sugars.

NATURE OF THE RESIDUE IN TOMATO	**PMRA #2376233, 2418187**
Radiolabel Position	[Phenyl-U-^{14}C] and [2,6-pyridyl-^{14}C]
Test Site	Tomato plants grown in individual pots and maintained in a plastic polytunnel.
Treatment	Three foliar spray applications at 31, 19 and 7 days prior to harvest.
Total Rate	3 × 100 g a.i./ha for a total rate of 300 g a.i./ha.
Formulation	30% suspension concentrate
Preharvest interval	7 days

Matrix	**PHI (days)**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**
		TRR (ppm)	**TRR (ppm)**
Tomato Fruit	7	0.170	0.193
Foliage	7	16.635	17.084

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**	**[Phenyl-U-^{14}C]**	**[2,6-pyridyl-^{14}C]**
Tomato Fruit	Pyriofenone	Pyriofenone	--	2MDPM
Foliage	Pyriofenone	Pyriofenone	2MDPM	--

Proposed Metabolic Scheme in Tomato:



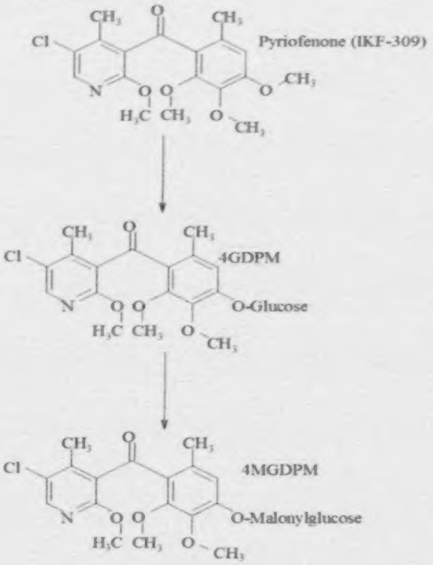
Metabolism of pyriofenone in tomato is proposed to result from hydrolysis of the phenyl ring methoxy groups yielding low amounts of the metabolite 2MDPM.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, carrot and spring wheat	**PMRA #2376520, 2418187**
Radiolabel Position	[Phenyl-U-^{14}C]
Test site	Plastic pots containing sandy loam soil maintained in a climate controlled room.
Formulation	30% soluble concentrate
Application rate and timing	Bare soil was treated at a rate of 284 g a.i./ha and aged for 31, 122 and 364 days. Samples of wheat forage, hay and grain/straw were harvested 45-58, 115-123 and 137-151 days post planting, and samples of carrots (roots and tops) and lettuce were harvested early at 102-115 and 70-74 days post planting, respectively, and later (final), at 136-161and 102-107 days post planting, respectively.
Metabolites Identified	**[Phenyl-U-^{14}C]**

PBI (days)	**Matrix**	**Major Metabolites (>10% of the TRRs)**	**Minor Metabolites (<10% of the TRRs)**
31	Wheat Forage	Pyriofenone	--
	Wheat Hay	Pyriofenone, 4GDPM, 4MGDPM	--
	Wheat Straw	Pyriofenone, 4GDPM, 4MGDPM	--

	Carrot Root (early)	Pyriofenone	--
	Carrot Root (final)	Pyriofenone	--
	Carrot Foliage (final)	Pyriofenone	--
122	Wheat Forage	Pyriofenone, 4MGDPM	--
	Wheat Hay	Pyriofenone, 4MGDPM	--
	Wheat Straw	Pyriofenone, 4MGDPM	--
	Carrot Root (early)	Pyriofenone	--
	Carrot foliage (early)	Pyriofenone	--
	Carrot Root (final)	Pyriofenone	--
	Carrot Foliage (final)	Pyriofenone	
364	Wheat Forage	Pyriofenone	--
	Wheat Hay	Pyriofenone, 4MGDPM	--
	Wheat Straw	Pyriofenone, 4GDPM	--
	Carrot Root (early)	Pyriofenone	--
	Carrot foliage (final)	Pyriofenone	--
	Carrot foliage (final)	Pyriofenone	--

Proposed Metabolic Scheme in Rotational Crops:



Metabolism in rotational crops is similar to primary crops and is proposed to result from methoxy group hydrolysis on the phenyl ring followed by conjugation with naturally occurring sugars.

NATURE OF THE RESIDUE IN ANIMALS	PMRA # N/A
Not required as there are no livestock feedstuffs associated with the approved and proposed uses.	

FREEZER STORAGE STABILITY	PMRA #1933882, 1978125, 2376514
Plant matrices: Grapes, wheat (grain and straw), summer squash The freezer storage stability data indicate that residues of pyriofenone are stable at ≤-10°C for 18 months in grapes and wheat matrices and for 9 months in summer squash. **Animal matrices:** Not required as there are no livestock feedstuffs associated with the approved and proposed uses.	

CROP FIELD TRIALS & RESIDUE DECLINE ON GRAPES (EU TRIALS)	PMRA #1933886, 1933883, 1933887, 1933885, 1933884
Seventeen grape field trials were conducted in Germany (four trials), Northern France (four trials), Southern France (four trials), Spain (three trials), and Italy (two trials) during the 2007, 2008, and 2009 growing seasons. Each field trial included one control plot and one treated plot. Treated plots received three foliar broadcast applications of a 300 g a.i./L suspension concentrate formulation (IKF-309 300SC) at application rates of 79.0-98.3 g a.i./ha/application, for total seasonal rates of 252-289 g a.i./ha. Retreatment intervals (RTIs) were 9-15 days. Applications were made in spray volumes of 366-875 L/ha; adjuvants were not used in any of the applications. Single control and duplicate treated samples of grapes (bunches) were	

harvested from each plot at preharvest intervals (PHIs) of 27-29 days; in the 2007 trials, only one treated sample was analyzed for each plot. At four 2007 trial sites and four 2008 trial sites, additional samples of grapes were collected to assess residue decline at 0, 14 (2008 trial sites only), 20-22, 34-35, and 41-44 (2007 trial sites only) days after last application (DALA); additional samples of grapes were also taken at 14 DALA at three 2009 trial sites to assess residue decline.

Residue decline data show that residues of pyriofenone decreased in cucurbits with increasing PHIs.

Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**n**	**Pyriofenone Residue Levels (ppm)**				
				LAFT	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Grape	252-289	27-29	30	0.02	0.14	0.07	0.07	0.03

LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON CUCURBITS – CUCUMBERS, CANTALOUPE, SUMMER SQUASH | **PMRA #2376515**

Twenty-eight field trials were conducted in Canada and the United States encompassing North American Free Trade Agreement (NAFTA) Growing Regions [a total of 9 cucumber trials covering regions 2, 3, 5 and 6; a total of 9 summer squash trials covering regions 1, 2, 3, 5, 10, and 12; and a total of 10 cantaloupe trials covering regions 2, 5, 6, and 10 during the 2012 growing season]. At each trial location, consisting of one untreated and one treated plot, four foliar ground applications of Pyriofenone 300SC at 6-8 day intervals were made to the treated plots at a target rate ~90 g a.i./ha for actual totals of 341-373 g a.i./ha. Non-ionic surfactant was added to the spray mixture for all applications. Cucurbits were collected at a PHI of 2.5-10 hours after the last application (i.e., 0-day PHI) and included three sites with decline studies (also sampled at 3, 7 and 9 or 10 days).

Residue decline data show that residues of pyriofenone decreased in cucurbits with increasing PHIs.

Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**n**	**Pyriofenone Residue Levels (ppm)**				
				LAFT	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Cucumber	342-368	0	9	0.011	0.062	0.034	0.034	0.017
Summer Squash	346-366	0	9	0.010	0.072	0.042	0.040	0.024
Cantaloupe	341-373	0	10	0.026	0.167	0.046	0.056	0.046

LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard

Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON BERRIES AND SMALL FRUITS – GRAPES, STRAWBERRIES, BLACKBERRIES, BLUEBERRIES, KIWIS	**PMRA #2376518**

Forty field trials were conducted in Canada and the United States encompassing NAFTA Growing Regions [a total of 12 grape trials covering regions 1, 5, 10, 11; a total of 9 strawberry trials covering regions 1, 3, 5, 10, and 12; a total of 10 blueberry trials {9 highbush and 1 lowbush in Zone 1}covering regions 1, 2, 5, 12; a total of 6 blackberry trials covering regions 2, 5, 6 and 12; and a total of 3 kiwi trials covering region 10] during the 2012 growing season. At each trial location, consisting of one untreated and one treated plot, four foliar ground applications of Pyriofenone 300SC at 6-8 day intervals were made at a target rate of 90 g a.i./ha, for a total ranging from 347-383 g a.i./ha, except for one strawberry site treated with only 123 g a.i./ha due to a miscalculation resulting in a total of 8 trials conducted at GAP. Adjuvants were added to the spray mixtures at 39 (absent from one grape site) of the 40 sites and berries were harvested at a 0-day PHI, 1-10 hours after the last application including the four sites with decline studies (also sampled at PHIs of 3, 7 and 10 days [grapes and strawberries], 3, 7 and 9 days [blueberries] and 7, 14 and 18 days [blackberries]).

Residue decline data show that residues of pyriofenone decreased in berries and small fruits with increasing PHIs.

Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**n**	**Pyriofenone Residue Levels (ppm)**				
				LAFT	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Grape	347-368	2-9	12	0.063	0.461	0.234	0.254	0.121
Strawberry	348-369	2.5-8	8	0.026	0.269	0.169	0.160	0.076
Highbush Blueberry	352-383	1-8	9	0.104	0.546	0.329	0.338	0.149
Lowbush Blueberry	347	10	1	0.635	0.635	-	-	-
Blackberry	347-367	4.5-9.5	6	0.068	0.474	0.272	0.287	0.143
Kiwi	356-372	8.5-9.5	3	0.047	0.606	0.134	0.262	0.275

LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.
§ Due to field operator error one site under applied the active ingredient.

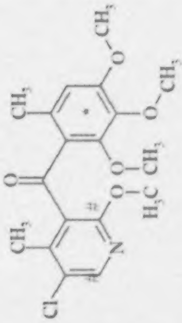
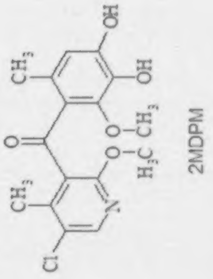
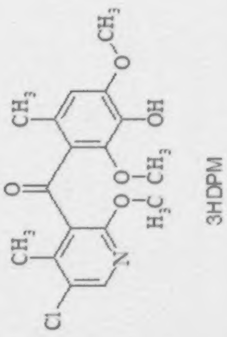
RESIDUE DATA IN ROTATIONAL CROPS	**PMRA # N/A**
Not required given that the regulated residue, pyriofenone, in edible crop matrices at the 12-month PBI in the confined crop rotational study was below the trigger value of 0.01 ppm.	
PROCESSED FOOD AND FEED - GRAPES	**PMRA #1933887, 1933885**
Test Site	Grape vines in test plots in Europe
Treatment	Three broadcast foliar spray applications at RTIs of 9-14 days
Rate	253-289 g a.i./ha (1x trials) and 785-787 g a.i./ha (3x trials)
End-use product/formulation	30% suspension concentrate
Preharvest interval	27-29 days
Processed Commodity	**Processing Factor**
Juice	0.2x
Raisins	2.9x
LIVESTOCK FEEDING	**PMRA # N/A**
Not required as there are no livestock feedstuffs associated with the approved and proposed uses.	

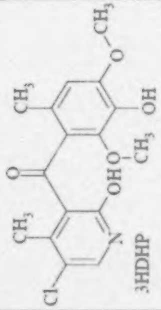
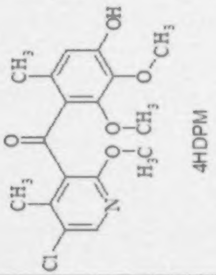
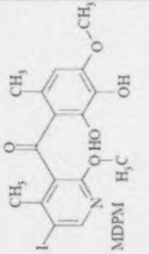
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

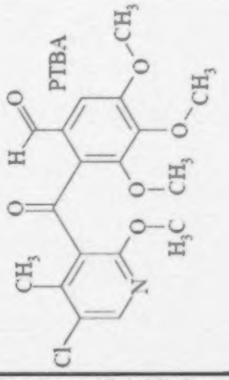
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT Primary crops (grape, wheat, tomato) Rotational crops (wheat, carrot, lettuce)	Pyriofenone
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops (grape, wheat, tomato) Rotational crops (wheat, carrot, lettuce)	Pyriofenone
METABOLIC PROFILE IN DIVERSE CROPS	Similar in grape, tomato and wheat.
ANIMAL STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT	N/A
RESIDUE DEFINITION FOR RISK ASSESSMENT	N/A
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	-
FAT SOLUBLE RESIDUE	N/A

DIETARY RISK FROM FOOD AND WATER			
Refined chronic non-cancer dietary risk ADI = 0.09 mg/kg bw/d Estimated chronic drinking water concentration = 1.17 µg a.i./L (Level I, surface water)	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
	All infants < 1 year	2.4	2.5
	Children 1–2 years	8.0	8.0
	Children 3 to 5 years	4.8	4.8
	Children 6–12 years	2.0	2.0
	Youth 13–19 years	0.8	0.8
	Adults 20–49 years	1.0	1.0
	Adults 50+ years	1.3	1.3
	Females 13–49 years	1.1	1.2
	Total population	1.5	1.6

Table 7 Summary of transformation products and unextracted residues observed in fate studies

Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)[2]
PARENT					
(IKF-309 pyriofenone)	(5-chloro-2-methoxy-4-methyl-3-pyridinyl) (2,3,4-trimethoxy-6-methylphenyl) methanone				
MAJOR (>10% applied radioactivity) TRANSFORMATION PRODUCTS					
2MDPM	(5-chloro-2-methoxy-4-methyl-3-pyridyl)(3,4-dihydroxy-2-methoxy-6-methylphenyl)ketone		Aerobic soil PMRA # 2376261	2.1 (90)	<0.8 (119)
			Anaerobic soil PMRA # 2376266	19.6 (120)	19.4 (150)
			Soil photolysis[1]		
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	8.5 (60)	3.4 (100
			Anaerobic aquatic PMRA # 2376270	13.5 (28)	4.62 (100)
			Field studies	Not monitored	Not monitored
3HDPM	(5-chloro-2-methoxy-4-methyl-3-pyridyl)(3-hydroxy-2,4-dimethoxy-6-methylphenyl)ketone		Aerobic soil PMRA # 2376261	3.6 (31)	1.6 (119)
			Anaerobic soil PMRA # 2376266	36.1 (75)	1.5 (150)
			Soil photolysis[1] PMRA # 2376255	3.4 (38.44)	3.4 (38.44)
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	8.4 (7)	1.6 (30)
			Anaerobic aquatic PMRA # 2376270	10.4 (14)	ND (100)
			Field studies	Not monitored	Not monitored
Carbon dioxide	CO_2		Aerobic soil PMRA # 2376261	28.7 (119)	28.7 (119)
			Anaerobic soil PMRA # 2376266	5.1 (120)	5.1 (120)

			Soil photolysis[1] PMRA # 2376255	10.5 (37.74)	10.5 (37.74)
			Aqueous photolysis[1]	9.6 (7)	9.6 (7)
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	16.8 (100)	16.8 (100)
			Anaerobic aquatic PMRA # 2376270	1.7 (100)	1.7 (100)
			Field studies	Not monitored	Not monitored
Unextracted residues			Aerobic soil PMRA # 2376261	68.5 (119)	68.5 (119)
			Anaerobic soil PMRA # 2376266	84.7 (120)	84.7 (120)
			Soil photolysis[1] PMRA # 2376255	7 (38.44)	7 (38.44)
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	84.4 (100)	84.4 (100)
			Anaerobic aquatic PMRA # 2376270	82.7 (56)	80.4 (100)
Minor (<10% applied radioactivity) TRANSFORMATION PRODUCTS					
3HDHP	(5-chloro-2-hydroxy-4-methyl-3-pyridyl)(3-hydroxy-2,4-dimethoxy-6-methylphenyl)ketone	 Cl CH3 O CH3 N OH O CH3 OH O CH3 3HDHP	Aerobic soil		
			Anaerobic soil		
			Soil photolysis[1]		
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	5.3 (14)	2.7 (100)
			Anaerobic aquatic		
			Field studies		
4HDPM	(5-chloro-2-methoxy-4-methyl-3-pyridyl)(4-hydroxy-2,3-dimethoxy-6-methylphenyl)ketone	 Cl CH3 O CH3 N O H3C O CH3 O CH3 OH 4HDPM	Aerobic soil PMRA # 2376261	3.2 (14)	0.7 (119)
			Anaerobic soil		
			Soil photolysis[1]		
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	1.4 (60)	< LOD (100)
			Anaerobic aquatic		
			Field studies		
4MDPM	(5-chloro-2-methoxy-4-methyl-3-pyridyl)(3,4-dihydroxy-2-methoxy-6-methylphenyl)ketone	 I CH3 O CH3 N O HO H3C OH O CH3 MDPM	Aerobic soil PMRA # 2376261		
			Anaerobic soil		
			Soil photolysis[1]		
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	4.4 (14)	< LOD (100)
			Anaerobic aquatic		

			Field studies		
PTBA	2-(5-chloro-2-methoxy-4-methylnicotinoyl)-3,4,5-trimethoxybenzaldehyde		Aerobic soil		
			Anaerobic soil		
			Soil photolysis[1]		
			Aqueous photolysis[1]		
			Hydrolysis		
			Aerobic aquatic PMRA # 2376268	3.5 (30)	< LOD (100)
			Anaerobic aquatic		
			Field studies		

[1] Photolysis studies were conducted under artificial light, and durations were converted to equivalent days of summer sunlight at 40° latitude following OECD draft Phototransformation of Chemicals on Soil Surfaces.

[2] %AR at the end of the study associated with the radiolabel with maximum %AR.

Table 8 Summary of the transformation rates of pyriofenone from soil

Test Material	Test Substance	Model	DT$_{50}$ (days)	DT$_{90}$ (days)	Chi[2] error	T_R[3]	Persistent Classification (PMRA)[1]
Phototransformation on soil (PMRA # 2376255)							
sandy loam	**IKF-309**	DFOP	186	876	3	297	Persistent
	IKF-309 + **3HDPM**	DFOP	222	988	2.8	330	Persistent
aerobic soil (PMRA # 2376261, PMRA # 2376263)							
Bromsgrove soil 20°C (sandy loam)	**IKF-309**	SFO	74.6	248	3.6	75	Moderately persistent
	IKF-309 + **4HDPM** + **3HDPM** + **2MDPM**	SFO	76.3	253	3.5	76.3	Moderately persistent
Evesham 3 soil 20°C (clay loam)	**IKF-309**	IORE	52	396	3.5	119	Moderately persistent
	IKF-309 +	IORE	54.8	398	3.5	120	Moderately persistent

Test Material	Test Substance	Model	DT_{50} (days)	DT_{90} (days)	Chi^2 error	T_R[3]	Persistent Classification (PMRA)[1]
	4HDPM + **3HDPM** + **2MDPM**						
Elmton soil 20°C (clay loam)	**IKF-309**	SFO	49	164	1.1	49	Moderately persistent
	IKF-309 + **4HDPM** + **3HDPM** + **2MDPM**	SFO	52.6	175	1	52.6	Moderately persistent
Elmton soil 10°C (clay loam)	**IKF-309**	SFO	135	448	2.3	135	Moderately persistent
	IKF-309 + **4HDPM** + **3HDPM** + **2MDPM**	SFO	141	468	2.6	141	Moderately persistent
Calke sandy loam	**IKF-309**	DFOP	155	642	1.4	210	Moderately persistent
	IKF-309 + **4HDPM** + **3HDPM** + **2MDPM**	DFOP	156	651	1.6	213[2]	Moderately persistent
Calke sandy loam Sterile (extracted IKF-309)	**IKF-309**	SFO	1659	5509	2.4	1659	Persistent
	IKF-309 + **4HDPM** +	SFO	1659	5509	2.4	1659	Persistent

Test Material	Test Substance	Model	DT_{50} (days)	DT_{90} (days)	Chi[2] error	T_R[3]	Persistent Classification (PMRA)[1]
	3HDPM + 2MDPM						
Anaerobic soil (PMRA # 2376266)							
DU soil (loam)	**IKF-309**	IORE	48.1	109	10	32.7	Moderately persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	66.9	222	8.1	66.9	Moderately persistent
MSL (Sandy clay loam)	**IKF-309**	IORE	34.5	81.1	11	24.4	Slightly persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	51.5	171	7.3	51.5	Moderately persistent
RMN (Sandy loam)	**IKF-309**	SFO	28.9	96	14	28.9	Slightly persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	59.1	196	6.9	59.1	Moderately persistent
PD (Sandy loam)	**IKF-309**	SFO	32.1	107	16	32.1	Slightly persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	74.2	247	6.5	74.2	Moderately persistent
Field dissipation studies (Ephrata: PMRA# 2376526, Northwood: PMRA# 2376534 and Kerman: PMRA# 2376528)							
Ephrata (Sand/sandy loam)	**IKF-309**	DFOP	275	1721	9.9	623	Persistent

Test Material	Test Substance	Model	DT_{50} (days)	DT_{90} (days)	Chi[2] error	T_R[3]	Persistent Classification (PMRA)[1]
Northwood (Loam/clay loam)	**IKF-309**	DFOP	0.4	654	25	289	Non-persistent
Kerman (Sandy loam/loamy sand)	**IKF-309**	IORE	53	513	12	154	Moderately persistent

[1] PMRA classification, according to the scheme of Goring *et al.* 1975

[2] Value used to calculate expected environmental concentrations

[3] T_R: Representative half-life used as an approximation of first-order kinetics for modelling purposes

Table 9 Summary of transformation products from laboratory soil degradation studies

Transformation product	Max. % AR[a] (day)	% AR at Study End (study length)[b]	Study (PMRA#) in which Max. AR was observed
Phototransformation on soil[c] (PMRA# 2376255)			
Major transformation products (>10% AR, or increasing at the end of the study)			
Carbon dioxide	10.5 (37.74)	10.5 (37.74)	2376255
Minor transformation products (<10% AR)			
Unextracted radioactivity	7 (37.74)	7 (37.74)	2376255
3HDPM	3.4 (38.44)	3.2 (27.32)	2376255
Component 1	3.9 (19.57)	2.7 (27.32)	2376255
Component 2	3.7 (19.57)	0.8 (27.32)	2376255
Component 3	3.3 (38.44)	2.5 (27.32)	2376255
Component 4	1.4 (27.32)	ND (4.06)	2376255
Component 6	1.3 (37.74)	1.3 (37.74)	2376255

Aerobic soil biotransformation (PMRA 2376261, and 2376263)			
Major transformation products (>10% AR, or increasing at the end of the study)			
Carbon dioxide	28.7 (119)	28.7 (119)	2376261
Unextracted residues	68.5 (119)	68.5 (119)	2376261
Minor transformation products (<10% AR)			
4HDPM	3.2 (14)	0.7 (119)	2376261
3HDPM	3.6 (31)	1.6 (119)	2376261
2MDPM	2.1 (90)	<0.8 (119)	2376261
A	9.1^{d} (60)	5.2^{e} (90)	2376261
B	7.1 (90)	2.8 (119)	2376261
C	1.5 (60)	0.9 (364)	2376263
E	1.1 (60)	<0.2 (364)	2376263
F	2.6 (31)	<0.1 (364)	2376263
Anaerobic soil biotransformation (PMRA # 2376266)			
Major transformation products (>10% AR, or increasing at the end of the study)			
Unextracted residues	84.7 (120)	84.7 (120)	2376266
3HDPM	36.1 (75)	1.5 (150)	2376266
2MDPM	19.6 (120)	19.4 (150)	2376266

Minor transformation products (<10% AR)			
Carbon dioxide	5.1 (120)	5.1 (120)	2376266
22.5 min.[f]	2.3 (60)	ND (150)	2376266

[a] Maximum Applied Radioactivity, both radiolabels

[b] % AR at study end associated with highest Max. % AR (i.e. not necessarily the max. concentration at study end)

[c] (day) and (study length) were estimated by comparing the light radiation from the lamp used in the study and the radiation from the sun during a mid-summer day at a 40°N latitude

[d] Component A was shown to be composed of six minor components, none of which accounted for greater than 4.0%

[e] Component A was shown to be composed of four minor components, none of which accounted for greater than 2.0%

[f] Degradation product eluting at this time in the chromatographic system

ND: Not detected or <0.1%

Table 10 Adsorption and desorption characteristics of IKF-309 on 5 soils at 20°C

Soil	Soil type	Soil pH ($CaCl_2$)	Organic carbon content (%)	Adsorption					Desorption		
				K_F^{ads}	K_{Foc}^{ads}	1/n	Mobility class		K_F^{des}	K_{Foc}^{des}	1/n
							McCall[1]	FAO[2]			
Bromsgrove	Sandy loam	4.6	0.7	12.5	1788	0.96	Low	SM	15.7	ND	0.90
Calke	Sandy loam	5.4	3.5	34.1	973	0.88	Low	MM	34.2	ND	0.81
Elmton	Sandy clay loam	7.0	4.3	29.3	681	0.86	Low	MM	30.2	ND	0.81
Evesham 3	Clay loam	7.3	1.6	19.1	1195	0.87	Low	SM	23.3	ND	0.86
Warsop	Loamy sand	4.3	0.5	13.3	2657	0.90	Slight	SM	18.6	ND	0.88

K_F^{ads}: Freundlich adsorption distribution coefficient

K_{Foc}^{ads}: Coefficient of adsorption per unit organic carbon

1/n: Exponent of the Freundlich adsorption or desorption isotherm

K_F^{des}: Freundlich desorption distribution coefficient

K_{Foc}^{des}: Coefficient of desorption per unit organic carbon

[1] McCall *et al.* (1981)

[2] FAO (2000): SM-Slightly Mobile; MM- Moderately Mobile

Table 11 **Pyriofenone levels (percent of peak concentration) at field study sites approximately one year after the last application, and at the end of the study.**

Field study (Soil)	% of peak concentration		PMRA#
	ca. one year (day)	End of study (day)	
Ephrata, WA, USA (Sand/loamy sand)	53% (365)	30% (540)	2376526
Northwood, ND, USA (Loam/clay loam)	15% (370)	8% (665)	2376534
Kerman, CA, USA (Sandy loam/loamy sand)	18% (362)	7% (543)	2376528

Table 12 **Maximum pyriofenone concentrations in the various depth horizons of field study sites [mg/kg soil (% max. concentration)[1]]**

Depth (cm)	Ephrata, WA, USA (sand/loamy sand)	Northwood, ND, USA (loam/clay loam)	Kerman, CA, USA (sandy loam/loamy sand)
0-7.6	0.1165 (100%)	0.3683 (100%)	0.1476 (100%)
7.6-15.2	0.0313 (26.9%)	0.0175 (4.7%)	0.001 (0.7%)
15.2-30.5	0.0127 (10.9%)	0.0028 (0.8%)	0 (0%)
30.5-45.7	0.0072 (6.2%)	0.0007 (0.2%)	0 (0%)
45.7-61	0 (0%)	0 (0%)	0 (0%)

[1] From single replicate

Table 13 **Summary of the transformation rates of pyriofenone for laboratory aquatic studies**

Test Material	Test Substance	Model	DT_{50} (days)	DT_{90} (days)	Chi^2 error	T_R	Persistent Classification (PMRA)[1]
Hydrolysis (PMRA # 2376252)							
50°C in sterile aqueous buffer solutions	**IKF-309**	No degradation					persistent

prepared at pH 4.0, 7.0 and 9.0							
Phototransformation in water (PMRA # 2376259)							
Natural water	**IKF-309**	SFO	20	66	7.3	19.8	Slightly persistent
Purified water	**IKF-309**	SFO	33	110	6.1	33	Slightly persistent
Aerobic water-sediment system (PMRA # 2376268)							
Calwich Abbey Lake (silt loam)	**IKF-309**	SFO	5.02	16.7	11	5.02	Non-persistent
	IKF-309 + 4HDPM + 3HDPM + 2MDPM	SFO	5.8	19.3	11	5.8	Non-persistent
Swiss Lake(sand)	**IKF-309**	SFO	14.2	47.1	10	14.2	Non-persistent
	IKF-309 + 4HDPM + 3HDPM + 2MDPM + PTBA + 3HDHP + 4MDPM	SFO	25.5	84.8	11	25.5[2]	Slightly persistent
Anaerobic water-sediment system (PMRA # 2376270)							
Tauton River (silt loam)	**IKF-309**	SFO	16.9	56.3	7.4	16.9	Slightly persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	23.7	78.6	4.5	23.7	Slightly persistent

Weweantic River (sand)	**IKF-309**	SFO	13.6	45	10	13.6	Non-persistent
	IKF-309 + 3HDPM + 2MDPM	SFO	21.5	71.5	7	21.5	Slightly persistent

[1] PMRA classification, according to the scheme of Goring *et al.* 1975
[2] Value used to calculate expected environmental concentrations

Table 14 Summary of transformation products for laboratory aquatic studies

Transformation product[a]	**Max. % AR**[b] **(day)**	**% AR at Study End (study length)**[c]
Phototransformation in water[d] **(PMRA# 2376259)**		
Major transformation products (>10% AR, or increasing at the end of the study)		
Carbon dioxide	9.6 (21)	9.6 (21)
Polar residues	23.8 (21)	23.8 (21)
Minor transformation products (<10% AR)		
Met A	2.9 (21)	2.9 (21)
Met B	0.8 (12)	0.21 (21)
Met C	1 (21)	1 (21)
Met D	3 (21)	3 (21)
PhDW2	1 (21)	1 (21)
PhDW3	1 (21)	1 (21)
PhDW4	1.2 (21)	1.2 (21)
PhDW5	0.8 (21)	0.8 (21)
PhDW6	0.6 (21)	0.6 (21)
PhDW7	1.2 (21)	1.2 (21)
PhDW8	0.4 (21)	0.4 (21)
PhDW9	0.5 (21)	0.5 (21)
PhDW10	0.2 (21)	0.2 (21)
PhDW11	0.3 (21)	0.3 (21)
PyDW1	2.4 (21)	2.4 (21)
PyDW2	1.2 (21)	1.2 (21)
PyDW3	0.8 (21)	0.8 (21)
PyDW4	1.8 (21)	1.8 (21)
PyDW5	2.2 (21)	2.2 (21)
PyDW6	1.8 (9)	1.1 (21)
PyDW7	0.7 (21)	0.7 (21)
PyDW8	0.6 (21)	0.6 (21)

PyNW1	4.9 (21)	4.9 (21)
PyNW3	2 (21)	2 (21)
PyNW4	2.1 (21)	2.1 (21)
PyNW5	1.9 (21)	1.9 (21)
PyNW6	1.1 (21)	1.1 (21)
PyNW7	2.4 (12)	1.1 (21)
PyNW8	1.1 (12)	0.9 (21)
PyNW9	0.6 (12)	0.6 (21)
PyDW10	2.1 (21)	2.1 (21)
PyDW11	0.3 (6)	0.3 (21)
Aerobic biotransformation in water-sediment (PMRA 2376268)		
Major transformation products (>10% AR, or increasing at the end of the study)		
Carbon dioxide	16.8 (100)	16.8 (100)
Unextracted residues	84.4 (100)	84.4 (100)
Minor transformation products (<10% AR)		
2MDPM	8.5 (60)	3.4 (100)
3HDHP	5.3 (14)	2.7 (100)
3HDPM	8.4 (7)	1.6 (30)
4HDPM	1.4 (60)	- (100)
4MDPM	4.4 (14)	- (100)
A (Rt 3-5 minutes)	7.9 (60)	- (100)
B (Rt 5-8 minutes)	6.4 (100)	6.4 (100)
C (Rt 9-12 minutes)	1.6 (60)	1.1 (100)
D (Rt 14 minutes)	1.8 (30)	- (100)
E (Rt 15 minutes)	2.1 (30)	- (100)
F (Rt 16 minutes)	3.8 (30)	- (100)
G (Rt 17'50 minutes)	6.8 (30)	- (100)
H (Rt 18-21 minutes)	6.5 (14)	3.2 (100)
I (Rt 20 minutes)	2.4 (30)	- (100)
J (Rt 22'10 minutes)	3.8 (30)	- (100)
K (Rt 23'0 minutes)	2.9 (30)	- (100)
L (Rt 24 minutes)	2.9 (30)	- (100)
M (Rt 27-30 minutes)	2.5 (14)	- (100)
N (Rt 34-37 minutes)	1.3 (30)	- (100)
O (Rt 41-43 minutes)	2.1 (14)	1 (30)
PTBA	3.5 (30)	- (100)

Anaerobic aquatic biotransformation (PMRA # 2376270)		
Major transformation products (>10% AR, or increasing at the end of the study)		
2MDPM	13.5 (28)	4.62 (100)
3HDPM	10.4 (14)	nd (100)
Unextracted residues	82.7 (56)	80.4 (100)
Minor transformation products (<10% AR)		
Carbon dioxide	1.7 (100)	1.7 (100)
2_PMRA2376270	3.9 (100)	3.9 (100)
3_PMRA2376270	1.9 (7)	nd (100)
6_PMRA2376270	1.4 (14)	nd (100)
7_PMRA2376270	2.4 (100)	2.4 (100)

[a] The study PMRA number was added by the evaluator to some vaguely named transformation products

[b] Maximum Applied Radioactivity, both radiolabels

[c] % AR at study end associated with highest Max. % AR (i.e. not necessarily the max. concentration at study end)

[d] (day) and (study length) were estimated by comparing the light radiation from the lamp used in the study and the radiation from the sun during a mid-summer day at a 40°N latitude

Table 15 Screening level estimated terrestrial and aquatic environmental concentrations (EECs) from pyriofenone sprayed at a rate of 4 × 90 g a.i./ha, with a 7 day interval between applications.

Exposure scenario	**Terrestrial EEC**		**Aquatic EEC (mg a.i./L)**	
	Soil exposure[1] (mg a.i./kg)	**Foliar exposure[2] (g a.i./ha)**	**15 cm water[3]**	**80 cm water[3]**
Direct overspray	0.155	201	0.185	0.035
Drift, 1 m from treated area (groundboom): 6% of direct overspray	0.0093	12	0.011	0.0021
Drift, 1 m from treated area (airblast late season): 74% of direct overspray	0.114	148	0.1365	0.0256

1 Soil EEC calculated using a soil half-life of 213 days , assuming a soil bulk density of 1.5 g/cm^3, and a 15 cm soil depth.

2 Foliar EEC calculated using a foliar half-life of 10 days.

3 Aquatic EEC calculated using a half-life of 25.5 days.

Table 16 Peak and 21-day average pore water concentrations (µg a.i./L) for pyriofenone

Scenario	Peak pore water conc.	21-d pore water conc.
BC	0	0
MB	1.01	0.98
ON	0.63	0.62
QC	0.90	0.87
PEI	3.2	3.2

Table 17 Expected Environmental Concentration (EEC) in vegetation and insects after a direct over-spray as food sources for birds and small wild mammals.

Environmental Compartment	Fresh/dry weight ratios	Maximum residue concentration		Mean residue concentration	
		Concentration fresh weight (mg a.i./kg)	Concentration dry weight (mg a.i./kg)	Concentration fresh weight (mg a.i./kg)	Concentration dry weight (mg a.i./kg)
short range grass	3.3	42.9	141.6	15.2	50.3
long grass	4.4	19.7	86.5	6.4	28.2
broadleaf plants	5.4	24.3	131.0	8.0	43.3
Insects	3.8	16.8	64.0	11.6	44.2
pods with seeds	3.9	2.6	10.2	1.2	4.8
grain and seeds	3.8	2.6	9.9	1.2	4.7
fruit	7.6	2.6	19.8	1.2	9.4

Pyriofenone 300SC: 360 g a.i./ha (90 g a.i./ha × 4)

Table 18 Effects of pyriofenone technical and Pyriofenone 300SC Fungicide on non-target organisms.

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Earthworms					
Earthworm *(Eisenia fetida)*	pyriofenone technical	14d Acute	LC_{50} > 978.8 mg a.i./kg soil	N/A	2376281

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Beneficial foliar dwelling arthropods					
Predatory Mite *(Typhlodromus pyri)*	Pyriofenone 300SC	7d Reproduction	LR_{50} > 1035 g a.i./ha	N/A	2376285
Parasitic Wasp *(Aphidius rhopalosiphi)*	Pyriofenone 300SC	48h Reproduction	LR_{50} > 1000 g a.i./ha	N/A	2376284
Pollinators (Honeybees)					
Honeybee *(Apis mellifera)*	pyriofenone technical	48h Acute oral and 48h Acute contact	LD_{50} > 100 µg a.i./bee	Relatively non-toxic	2376283
Honeybee *(Apis mellifera)*	pyriofenone technical	10d Chronic	NOAEL = 27 µg a.i./bee[2]	N/A	2502015
Honeybee *(Apis mellifera)*	pyriofenone technical	Single exposure; 72 h Honeybee larvae toxicity	LD_{50} > 100 µg a.i./bee	N/A	2551864
Birds					
Bobwhite Quail *(Colinus virginianus)*	pyriofenone technical	single dose Acute oral	LD_{50} > 1958 mg a.i./kg bw/day	Practically non-toxic. No mortalities were observed during the test.	2376309
Canary *(Serinus canaria)*	pyriofenone technical	single dose Acute oral	LD_{50} > 2000 mg a.i./kg bw/day	Practically non-toxic. No mortalities were observed during the test.	2376318
Bobwhite Quail *(Colinus virginianus)*	pyriofenone technical	5d Dietary	LD_{50} > 980 mg a.i./kg bw/day	Practically non-toxic. No mortalities were observed during the test.	2376320

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Mallard Duck *(Anas platyrhynchos)*	pyriofenone technical	5d Dietary	LD_{50} > 1290 mg a.i./kg bw/day	Practically non-toxic. No mortalities were observed during the test.	2376322
Bobwhite Quail *(Colinus virginianus)*	pyriofenone technical	22w Reproduction	NOAEL = 96 mg a.i./kg bw/day	No adverse effects on any of the study endpoints were observed.	2376324
Mallard Duck *(Anas platyrhynchos)*	pyriofenone technical	23w Reproduction	NOAEL = 120 mg a.i./kg bw/day	No adverse effects on any of the study endpoints were observed.	2376327
Mammals					
Rat *(Rattus norvegicus)*	pyriofenone technical	Single dose; 14d Acute	LD_{50} > 2000 mg a.i./kg bw/day	Practically non toxic	1933846
Rat *(Rattus norvegicus)*	pyriofenone technical	2 Generations Reproduction	NOAEL = 334 mg a.i./kg bw/day	No effects on reproduction were observed	1933862
Terrestrial vascular plant					
Monocots & Dicots *(Various)*	Pyriofenone 300SC	21d Seedling emergence	ER_{25} > 360 g a.i./ha	N/A	2376335
Monocots & Dicots *(Various)*	Pyriofenone 300SC	21d Vegetative vigor	ER_{25} > 360 g a.i./ha	N/A	2376337
Freshwater Algae and macrophites					
Algae *Pseudokircheriella subcapitata* (Reclassified as *Raphidocelis subcapitata*)	pyriofenone technical	96h Inhibition	EC_{50} = 0.340 mg a.i./L	Most sensitive endpoint: area under growth curve	2376330

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Blue-green Algae *(Anabaena flos aquae)*	pyriofenone technical	96h Inhibition	EC_{50} = 0.062 mg a.i./L. [4]	Based on growth rate and area under the curve.	2376331
Diatom *(Navicula pelliculosa)*	pyriofenone technical	96h Inhibition	EC_{50} > 1.669 mg a.i./L	Endpoints affected: area under the growth curve, growth rates and yield	2376332
Duckweed *(Lemna gibba)*	pyriofenone technical	7d Inhibition	EC_{50} > 1.574 mg a.i./L	No statistically significant inhibition was observed for any of the measured growth parameters	2376334
Marine Algae					
Marine diatom *(Skeletonema costatum)*	pyriofenone technical	96h Inhibition	EC_{50} > 1.349 mg a.i./L;	Inhibition was less than 50% in any measurement parameter; area under the growth curve was the most, growth rates and yield The extrapolated EC_{50} was 2428, which is greater than the limit of solubility.	2376333
Freshwater invertebrates					
Water Flea *(Daphnia magna)*	Pyriofenone 300SC	48h Acute	LC_{50} = 36.8 mg a.i./L	Slightly toxic	2376289
Water Flea *(Daphnia magna)*	pyriofenone technical	48h Acute	LC_{50} > 1.55 mg a.i./L	No mortalities observed at highest concentration[3]	2376287
Water Flea *(Daphnia magna)*	pyriofenone technical	21d Chronic	NOEC = 0.0899 mg a.i./L	Based on effects on reproduction	2376291

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Midge larvae *(Chironomus riparius)*	pyriofenone technical	28d Emergence	NOEC > 0.0925 mg a.i./L (pore water); > 0.833 mg a.i./L overlying water	No test endpoints affected	2376293
Marine invertebrates					
Mysid *(Americamysis bahia)*	pyriofenone technical	96h Acute	LC_{50} = 0.79 mg a.i./L	Highly toxic	2376294
Eastern oyster *(Crassostrea virginica)*	pyriofenone technical	96h Mollusk shell deposition	EC_{50} = 1.10 mg a.i./L	N/A	2376295
Mysid *(Americamysis bahia)*	pyriofenone technical	30d (G1), 96h (G2) Reproduction	NOEC = 0.033 mg a.i./L	Based on effects on reproduction Compared to negative control, LOEC = 33 µg a.i./L (USEPA endpoint: NOEC < 33 ug a.i./L)	2545757
Marine amphipod *(Leptocheirus plumulosus)*	pyriofenone technical	10d Acute	LC_{50} = 0.491 mg a.i./L (pore water); 0.353 mg a.i./L (overlying water)	Highly toxic	2551865
Freshwater fish					
Rainbow trout *(Onchorynchuys mykiss)*	Pyriofenone 300SC	96h Acute/cold water fish	LC_{50} = 13.7 mg a.i./L	N/A	2376300

Species	Test material	Exposure	Endpoint	Degree of toxicity[1]/comments	Reference (PMRA#)
Rainbow trout *(Onchorynchuys mykiss)*	pyriofenone technical	96h Acute/cold water fish	LC_{50} > 1.44 mg a.i./L	No mortalities in any group; some sub-lethal toxic effects observed at the highest concentration (*3)	2376297
Common carp (*Cyprinus carpio*)	pyriofenone technical	96h Acute/warm water fish	LC_{50} > 1.41 mg a.i./L	No mortality at the highest tested concentration.[3]	2376302
Fathead minnow *(Pimephales promelas)*	pyriofenone technical	96h Acute/cold water fish	LC_{50} > 1.15 mg a.i./L; NOEC = 1.15 mg a.i./L	No mortality or sub-lethal effects were observed in any group.[3]	2542059
Fathead minnow *(Pimephales promelas)*	pyriofenone technical	33d Chronic Early Life Stage (ELS)	NOEC = 0.403 mg a.i./L	Survival and growth (length and wet weight)	2542060
Marine fish					
Sheepshead Minnow *(Cyprinodon variegatus)*	pyriofenone technical	96h Marine fish	LC_{50} > 1.27 mg a.i./L	No mortalities or sublethal effect observed at highest concentration.[3]	2376303
Sheepshead Minnow *(Cyprinodon variegatus)*	pyriofenone technical	34d Chronic (ELS)	NOEC = 0.293 mg a.i./L	Growth (wet and dry weight, length)	2542061

[1] USEPA classification (1985), Atkins *et al.* (1981); where applicable.

[2],There was no clear dose response relationship despite a 300 fold increase in dose, suggesting that the effects could be partially caused by the solvent.

[3] The highest test concentration was limited by pyriofenone's low solubility in water (1.56 mg/L).

[4] A sound $E_{Yeild}C_{50}$ value could not be determined from the complete dataset. Overall, cell yield was the most sensitive endpoint and followed a dose-response among the five lowest treatment groups (5.7, 14, 36, 91 and 224 µg a.i./L); however, the magnitude of inhibition (percent compared to the control) decreased with increasing IKF-309 concentration at the two highest treatment groups (565 and 1413 µg a.i./L). A conservative $E_{Yeild}C_{50}$ value of 0.062 mg a.i./L, calculated omitting the two higher treatment groups.

Table 19 **Risk to soil dwelling organisms as a result of direct in-field exposure.**

Organism	Exposure	Test Substance	Endpoint Value (mg a.i./kg soil d.w.)	EEC (mg a.i./kg soil dw)	RQ	LOC Exceeded?
Earthworm *(Eisenia fetida)*	14 d Acute	Pyriofenone technical	> 978.8	0.155	<0.01	No

Table 20 **Screening level risk to foliar-dwelling organisms as a result of direct in-field exposure.**

Application scenario		EEC (g a.i./ha)	RQ		LOC exceeded?
			Parasitoid wasp (*A. rhopalosiphi*) 48h-LR_{50} > 1000 g a.i./ha	Predatory mite (*T. pyri*) 14d-LR_{50} > 1035 g a.i./ha	
In-field	Direct foliar application: 4×90 g a.i./ha, 7-d interval	201	< 0.2	< 0.2	No (LOC = 2)

Table 21 **Screening Level EECs and RQ values for honeybees based on foliar and soil applications.**

Exposure route	EEC (μg a.i./g)	Exposure to bee (μg a.i./bee/day)	Endpoint (μg a.i./bee)	RQ	LOC exceeded?
Foliar Spray Application at rate of 110 g a.i./ha					
Adult acute contact	-	0.264	LD_{50} >100	<0.01	No (LOC=0.4)
Adult oral acute	10.78	3.14	LD_{50} >100	<0.03	No (LOC=0.4)
Larval oral acute	10.78	1.34	LD_{50} >100	<0.01	No (LOC=0.4)
Adult oral chronic	10.78	3.14	NOAEL = 27	0.12	No (LOC=1)

Table 22 **Risk to birds and mammals as a result of direct on-field exposure assuming a use pattern of 4 × 90 g a.i./ha (7 day interval), Pyriofenone 300SC Fungicide**

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[a] (mg a.i./kg bw)	RQ	LOC exceeded?
Small Bird (0.02 kg)					
Acute (LD_{50}/10)	> 195.8	Insectivore	16.32	< 0.08	No
Reproduction (NOAEL)	96	Insectivore	16.32	0.17	No
Medium Sized Bird (0.1 kg)					
Acute (LD_{50}/10)	> 195.8	Insectivore	12.74	< 0.07	No
Reproduction (NOAEL)	96	Insectivore	12.74	0.13	No
Large Sized Bird (1 kg)					
Acute (LD_{50}/10)	> 195.8	Herbivore (short grass)	8.23	< 0.04	No
Reproduction (NOAEL)	96	Herbivore (short grass)	8.23	0.09	No
Small Mammal (0.15 kg)					
Acute (LD_{50}/10)	> 200	Insectivore	9.39	< 0.05	No
Reproduction (NOAEL)	334	Insectivore	9.39	0.03	No
Medium Sized Mammal (0.35 kg)					
Acute (LD_{50}/10)	> 200	Herbivore (short grass)	18.21	< 0.09	No
Reproduction (NOAEL)	334	Herbivore (short grass)	18.21	0.15	No
Large Sized Mammal (1 kg)					
Acute (LD_{50}/10)	> 200	Herbivore (short grass)	9.73	< 0.05	No
Reproduction (NOAEL)	334	Herbivore (short grass)	9.73	0.03	No

a EDE = Estimated daily exposure; is calculated using the following formula: (FIR/bw) × EEC. Where FIR is Food Ingestion Rates (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{bw in g})^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$
At the screening level, food items representing the most conservative EEC for each size guild are used.

Table 23 **Risk assessment of Pyriofenone 300SC Fungicide to non-target terrestrial vascular plants at a maximum seasonal application of 360 g a.i./ha.**

Exposure	**Endpoint ER_{25} (g a.i./ha)**	**EEC (g a.i./ha)**	**RQ**	**LOC exceeded?**
Seedling emergence	>360	360	< 1	No
Vegetative vigour	>360	360	< 1	No

Table 24 **Screening level risk pyriofenone and Pyriofenone 300SC Fungicide to aquatic organisms.**

Organism (PMRA#)	**Test Substance**	**Exposure**	**Endpoint Value (mg a.i./L)**	**EEC (mg a.i./L)**	**RQ**	**LOC Exceeded ?**
Freshwater Species						
Algae						
Algae *Pseudokircheriella subcapitata* (Reclassified as *Raphidocelis subcapitata*) [2376330]	pyriofenone technical	96h	$EC_{50}/2 = 0.17$ mg a.i./L	0.035 mg a.i./L	0.20	No
Blue-green Algae (*Anabaena flos aquae*) [2376331]	pyriofenone technical	96h	$EC_{50}/2 = 0.031$ mg a.i./L	0.035 mg a.i./L	1.1	Yes
Diatom (*Navicula pelliculosa*) [2376332]	pyriofenone technical	96h	$EC_{50}/2 > 0.83$ mg a.i./L	0.035 mg a.i./L	< 0.04	No
Plants						
Duckweed (*Lemna gibba*) [2376334]	pyriofenone technical	7d	$EC_{50}/2 > 0.787$ mg a.i./L	0.035 mg a.i./L	< 0.04	No
Invertebrates						
Water Flea (*Daphnia magna*) [2376289]	Pyriofenone 300SC	48h	$LC_{50}/2 = 18.4$ mg a.i./L	0.035 mg a.i./L	<0.01	No

Organism (PMRA#)	Test Substance	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC Exceeded?
Water Flea (*Daphnia magna*) [2376287]	pyriofenone technical	48h	LC_{50}/2 > 0.775 mg a.i./L	0.035 mg a.i./L	< 0.04	No
Water Flea (*Daphnia magna*) [2376291]	pyriofenone technical	21d	NOEC/1 = 0.089 mg a.i./L	0.035 mg a.i./L	0.4	No
midge larvae (*Chironomus riparius*) [2376293]	pyriofenone technical	28d	NOEC: overlying water > 0.833 mg a.i./L; pore water: 0.0925 mg a.i./L	Overlying water: 0.035 mg a.i./L 21d pore water: 0.0032 mg a.i./L	Overlying water: 0.04 Pore water: 0.03	No
Fish						
Rainbow trout (*Onchorynchuys mykiss*) [2376300]	Pyriofenone 300SC	96h	LC_{50}/10 = 1.37 mg a.i./L	0.035 mg a.i./L	0.03	No
Rainbow trout (*Onchorynchuys mykiss*) [2376297]	pyriofenone technical	96h	LC_{50}/10 > 0.144 mg a.i./L	0.035 mg a.i./L	< 0.2	No
Common carp (*Cyprinus carpio*) [2376302]	pyriofenone technical	96h	$LC_{50}/10^{1}$ > 0.141 mg a.i./L	0.035 mg a.i./L	< 0.2	No
Fathead minnow (*Pimephales promelas*) [2542059]	pyriofenone technical	96h	$LC_{50}/10^{1}$ > 0.115 mg a.i./L	0.035 mg a.i./L	< 0.3	No
Fathead minnow (*Pimephales promelas*) [2542060]	pyriofenone technical	33d	NOEC/1=0.403	0.035 mg a.i./L	0.09	No

Organism (PMRA#)	**Test Substance**	**Exposure**	**Endpoint Value (mg a.i./L)**	**EEC (mg a.i./L)**	**RQ**	**LOC Exceeded ?**
Amphibians						
Fathead minnow (*Pimephales promelas*) as surrogate for Amphibians [2542059]	pyriofenone technical	96h	$LC_{50}/10^{1} >$ 0.115 mg a.i./L	0.185 mg a.i./L	<1.6	Yes[1]
Sheepshead Minnow (*Cyprinodon variegatus*) as surrogate for Amphibians [2542061]	pyriofenone technical	33d	NOEC/1=0.293	0.185 mg a.i./L	0.63	No
Marine Species						
Algae						
Marine diatom (*Skeletonema costatum*) [2376333]	pyriofenone technical	96h	$EC_{50}/2 >$ 0.6745 mg a.i./L	0.035 mg a.i./L	< 0.05	No
Invertebrates						
Eastern oyster (*Crassostrea virginica*) [2376295]	pyriofenone technical	96h	$EC_{50}/2 = 0.55$ mg a.i./L	0.035 mg a.i./L	0.06	No
Mysid (*Americamysis bahia*) [2376294]	pyriofenone technical	96h	$LC_{50}/2 =$ 0.395 mg a.i./L	0.035 mg a.i./L	0.09	No
Mysid (*Americamysis bahia*) [2545757]	pyriofenone technical	30d (G1), 96h (G2)	NOEC/1 = 0.033 mg a.i./L	0.035 mg a.i./L	1.04	Yes[2]
Marine amphipod (*Leptocheirus plumulosus*) [2551865]	pyriofenone technical	10d	$LC_{50}/2 = 0.18$ mg a.i./L overlying water; 0.246 mg a.i./L Peak pore water	Overlying water: 0.035 mg a.i./L Peak pore water: 0.0032 mg a.i./L	Overlying water: 0.19 Peak pore water 0.01	No

Organism (PMRA#)	Test Substance	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC Exceeded ?
Fish						
Sheepshead minnow (*Cyprinodon variegatus*) [2376303]	pyriofenone technical	96h	LC_{50}/10 > 0.127 mg a.i./L	0.035 mg a.i./L	< 0.3	No
Sheepshead minnow (*Cyprinodon variegatus*) [2542061]	pyriofenone technical	34d (ELS)	NOEC = 0.293 mg a.i./L	0.035 mg a.i./L	0.1	No

[1] No mortalities were observed up to the highest concentration. The achievable test concentrations were limited by the low solubility of the active ingredient in water.

[2] Risk is not expected for chronic exposure to marine invertebrates given the marginal exceedance of the LOC of 1.0 and the conservative assumptions for marine exposure.

Table 25 Tier I Refined risk assessment of Pyriofenone 300SC Fungicide to blue-green algae, mysid and amphibians.

Organism	Exposure	Endpoint (mg a.i./L)	On field		Off-field			
			Direct overspray		6% drift (ground spray, medium droplets)		74% drift (airblast fine droplets)	
			EEC (mg a.i./L)	RQ	EEC (mg a.i./L)	RQ	EEC (mg a.i./L)	RQ
Blue-green Algae (*Anabaena flos aquae*) [2376331]	96h	EC50 /2 = 0.031 mg a.i./L	0.035 mg a.i./L	1.1	0.0021	0.06	0.0256	0.83
Mysid (*Americamysis bahia*) [2545757]	30d (G1), 96h (G2)	NOEC/1 = 0.033 mg a.i./L	0.035 mg a.i./L	1.04	0.0021	0.06	0.0256	0.78

Table 26 Registered Alternatives (as of December 2014)

Crop / Crop group	Disease	Active Ingredient and Resistance Management Group
Cucurbits Vegetables Crop Group 9	Powdery mildew	Azoxystrobin (11) + Difenoconazole (3) Folpet (M) Myclobutanil (3) Potassium bicarbonate[x] *Bacillus subtillis* strain QST 713 (44)[x] Boscalid (7) + Pyraclostrobin (11) Pyraclostrobin (11) Chlorothalonil (M) Garlic Powder [x] Difenoconazole (3) Penthiopyrad (7) Penthiopyrad (7) + Chlorothalonil (M) Tea tree oil [x] Extract of *Reynoutria sachalinensis* [x] *Streptomyces lydicus* strain WYEC108 [x] Trifloxystrobin (11)
Berry and Small Fruit, Crop Group 13-07, except large shrub/tree berry subgroup 13-07C	Powdery mildew	Sulphur (M) Copper (M) Myclobutanil (3) Boscalid (7) + Pyraclostrobin (11) Quinoxyfen (13) Trifloxystrobin (11) Tetraconazole (3) Fluopyram (7) Fluopyram (7) + Pyrimethanil (9) Garlic Powder [x] Mancozeb (M) + Dinocap (U) Calcium polysulphide (M) Kresoxim-Methyl (11) Metrafenone (U8) Difenoconazole (3) Potassium bicarbonate[x] Tea tree oil [x] Mineral oil [x] *Bacillus subtilis* strain QST 713 (44) [x] *Streptomyces lydicus* strain WYEC108 [x]

Note the active might not be registered for all crops within the crop group.

[x] Non-conventional pesticides.

Table 27 List of Supported Uses

Proposed label claim	Supported use claim
Control of Powdery mildew (caused by *Podosphaera xanthii* or *Erysiphe cichoracearum*) / Cucurbits Crop Group 9 / 0.3 to 0.366 L Product/ha	Accepted as proposed (for control of *Podosphaera xanthii* and *Erysiphe cichoracearum* on cucurbits Crop Group 9)
Control of Powdery mildew (caused by *Erysiphe necator* / Grapes / 0.3 to 0.366 L Product/ha	Accepted as proposed (for control of *Erysiphe necator* on grapes)
Control of Powdery mildew (caused by *Podosphaera aphanis* / Strawberries / 0.3 to 0.366 L Product/ha	Accepted for Suppression of *Podosphaera aphanis* on strawberries
Control of Powdery mildew (caused by *Sphaerotheca macularis)* / Caneberries/ 0.3 to 0.366 L Product/ha	Accepted for Suppression of *Sphaerotheca macularis* on caneberries
Control of Powdery mildew (caused by *Sphaerotheca macularis)* / Goose berries/ 0.3 to 0.366 L Product/ha	Accepted for Suppression of *Sphaerotheca macularis* on goose berries
Control of Powdery mildew (caused by *Podosphaera clandestina)* / Saskatoon berries/ 0.3 to 0.366 L Product/ha	Accepted for Suppression of *Podosphaera clandestina* on Saskatoon berries

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Pyriofenone is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for pyriofenone in Canada are the same as corresponding tolerances to be promulgated in the United States.

Once established, the American tolerances for pyriofenone will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for pyriofenone in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 compares the MRLs proposed for pyriofenone in Canada with corresponding American tolerances and Codex MRLs. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Crop Group 9 - Cucurbit Vegetables	0.3	0.3	Not established
Crop Subgroup 13-07B: Bushberries	1.5	1.5	Not established
Crop Subgroup 13-07D: Small fruits vine climbing	1.5	1.5	Not established
Crop Subgroup 13-07A: Caneberries	0.9	0.9	Not established
Crop Subgroup 13-07G: Low growing berries	0.5	0.5	Not established

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

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[10] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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2376211	2013, IKF-309 - five batch analysis- alternate manufacturing site for technical pyriofenone, DACO: 2.13.3 CBI
2418188	2014, MSDS – [CBI removed], DACO: 2.11.2 CBI
2418189	2014, MSDS – [CBI removed], DACO: 2.11.2 CBI
2418190	2014, MSDS – [CBI removed], DACO: 2.11.2 CBI
2418191	2014, MSDS – [CBI removed], DACO: 2.11.2 CBI
2418192	2014, MSDS – [CBI removed], DACO: 2.11.2 CBI
2376240	2011, Independent Laboratory Validation (ILV) of the Residue Analytical Method for Detection of IKF-309 in Soil (RCC Study #B18843), DACO: 8.2.2.1,8.2.2.2
2376243	2007, validation of a residue analytical method for the determination of ikf-309 in agricultural soil, DACO: 8.2.2.1,8.2.2.2
2376247	2010, IKF-309 validation of methodology for the determination of residues in surface and drinking water, DACO: 8.2.2.3
2407105	2014, Independent Laboratory Validation of Ishihara Sangyo Kaisha (ISK) Residue Analytical Method for IKF-309 Determination of Residues in Surface Water, DACO: 8.2.2.3
2376479	2013, Part 3 Chemistry for Registration of End-Use Product - Pyriofenone 300SC Fungicide - 3.1 Product Identification, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4
2376481	2013, product chemistry studies for pyriofenone 300sc - series 61 - product identity and composition - description of materials used to produce the product - description of formulation process - discussion of formation of impurities, DACO: 3.2.1,3.2.2,3.2.3 CBI
2376483	2013, product chemistry studies for pyriofenone 300sc - series 62 -, DACO: 3.3.1,3.4,3.4.1 CBI
2376484	2011, product chemistry studies for pyriofenone 300SC (IKF-309) - SERIES 63 -, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9

2.0 Human and Animal Health

PMRA Document Number	Reference
1933845	2010, Pyriofenone Toxicology Summary - PMRA Submission, DACO: 4.1,6.1
1933846	2008, IKF-309 Technical: acute oral toxicity to the rat (acute toxic class method), DACO: 4.2.1
1933847	2009, IKF-309: Toxicity study by dietary administration to CD-1 mice for 13 weeks, DACO: 4.3.1
1933848	2010, IKF-309 Technical: repeated dose 90-day oral toxicity study in rats, DACO: 4.3.1
1933849	2010, IKF-309 Technical: repeated dose 90-day oral toxicity study in dogs, DACO: 4.3.2
1933850	2010, IKF-309 Technical: repeated dose 1-year oral toxicity study in rats, DACO: 4.4.1
1933852	2010, IKF-309 Carcinogenicity study by dietary administration to CD-1 mice for 78 weeks, DACO: 4.4.3
1933854	2010, IKF-309 Technical: Carcinogenicity Study in Rats, DACO: 4.4.3
1933858	2010, IKF-309 Technical: repeated dose 1-year oral toxicity study in dogs, DACO: 4.4.5
1933859	2010, 4-Week dietary immunotoxicity study in the female rat, DACO: 4.5
1933860	2010, IKF-309: 4-Week dietary immunotoxicity study in the female mouse, DACO: 4.5
1933861	2009, IKF-309 Technical: a reproduction toxicity study in rats a dose range-finding study, DACO: 4.5.1
1933862	2009, IKF-309 Technical: a reproduction toxicity study in rats, DACO: 4.5.1
1933863	2009, IKF-309: Dose range and time to peak effect in rats by acute oral administration, DACO: 4.5.12
1933864	2010, IKF-309: Neurotoxicity study by a single oral gavage administration to CD rats followed by a 14 day observation period, DACO: 4.5.12
1933865	2010, IKF-309: Neurotoxicity study by dietary administration to CD rats for 13 weeks, DACO: 4.5.13
1933866	2009, IKF-309 Technical: a teratogenicity study in rats a dose range-finding study, DACO: 4.5.2
1933867	2010, IKF-309 Technical: a teratogenicity study in rats, DACO: 4.5.2
1933868	2010, IKF-309 Technical: teratogenicity study in rabbits preliminary study, DACO: 4.5.3
1933869	2009, IKF-309 Technical: teratogenicity study in rabbits, DACO: 4.5.3
1933870	2007, IKF-309 Technical bacterial reverse mutation test, DACO: 4.5.4
1933871	2008, IKF-309 Technical in vitro mutation test using mouse lymphoma L5178Y cells, DACO: 4.5.5
1933872	2008, IKF-309 Technical in vitro mammalian chromosome aberration test in CHL cells, DACO: 4.5.6
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2055027	2011, Response to request for historical control data IKF-309 technical: repeated dose 90-day oral toxicity study in rats (MRID #48112816), DACO: 4.3.1
2055028	2011, Response to request for historical control data IKF-309 technical: repeated dose 90-day oral toxicity study in dogs (MRID #48112817), DACO: 4.3.2
2055029	2011, Response to request for historical control data IKF-309 technical: repeated dose 1-year oral toxicity study in rats (MRID #48125901), DACO: 4.3.8
2091200	2011, Historical data on abortion and premature delivery in KblJW rabbits, DACO: 4.5.3
2376213	2008, IKF-309 Technical: Acute Dermal Toxicity to the Rat, DACO: 4.2.2
2376215	2008, IKF-309 Technical: an acute (4-hour) inhalation toxicity study in the rat via nose-only exposure (amended), DACO: 4.2.3
2376218	2008, IKF-309 Technical: eye irritation to the rabbit, DACO: 4.2.4
2376222	2008, IKF-309 Technical: Skin Irritation to the Rabbit, DACO: 4.2.5
2376224	2009, IKF-309 Technical : Skin Sensitisation Study in Mice -Local Lymph Node Assay-, DACO: 4.2.6
2376227	2010, IKF-309: Toxicity study by dermal administration to CD rats for 4 weeks, DACO: 4.3.5
2407020	2008, IKF-309 Technical: acute oral toxicity to the rat (acute toxic class method), DACO: 4.2.1
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1933875	2010, DACO 6.1 Pyriofenone (IKF-309) - Summary of Metabolism in Animals (Goats) and Plants (Grape), DACO: 6.1
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1933877	2009, IKF-309 metabolism in grapes, DACO: 6.3
1933878	2010, DACO 7.1 Pyriofenone (IKF-309) - Summary of Residue Studies in Plants (Grape), DACO: 7.1
1933879	2008, validation of methodology for the determination of residues in wheat (grain and straw) and grapes, DACO: 7.2.1,7.2.2
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1933883	2009, residue study (at harvest) with ikf-309 300SC (ibe 3985) applied to wine grapes in southern france in 2008, DACO: 7.4.1
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1933885	2009, IKF-309 300SC residue study (at harvest and processing) with ikf-309 300SC (ibe 3985) applied to wine grapes in northern and southern france in 2008, DACO: 7.4.1,7.4.5
1933886	2008, residue study (decline) with ikf-309 300SC (ibe 3985) applied to wine grapes in germany and southern france in 2007, DACO: 7.4.1,7.4.2
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2376235	2013, IKF-309: radiovalidation of the extraction efficiency of the residue analytical method for crops, DACO: 7.2.3
2376514	2013, freezer storage stability of IKF-309 in squash, DACO: 7.3
2376515	2013, magnitude of residue of IKF-309 on cucurbits – usa & canada IN 2012, DACO: 7.4.1,7.4.2
2376518	2013, Magnitude of Residues of IKF-309 on the Berry Group – USA and Canada in 2012, DACO: 7.4.1,7.4.2
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2418187	2015, Response to Request for Additional Information for IKF-309 Metabolism in Tomatoes (MRID #49256110), Wheat (MRID# 49256109), and Rotational Crops (MRID# 49256115), DACO: 6.3 & 7.4.3
2376505	2009, IKF-309 300SC Dermal Penetration, DACO: 5.8.
2376507	2013, Dislodgeable Foliar Residue Study IKF-309 on Grapes – USA in 2012, DACO: 5.9(A)
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2376243	2007, validation of a residue analytical method for the determination of ikf-309 in agricultural soil, DACO: 8.2.2.1,8.2.2.2
2376247	2010, IKF-309 validation of methodology for the determination of residues in surface and drinking water, DACO: 8.2.2.3
2376252	2009, IKF-309 Hydrolysis in Water, DACO: 8.2.3.2
2376255	2007, IKF-309 soil photolysis (amended final report), DACO: 8.2.3.3.1
2376259	2010, IKF-309 Photodegradation in Water and Determination of the Quantum Yield, DACO: 8.2.3.3.2
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2376263	2008, IKF-309 Route of Degradation in Aerobic Soil, DACO: 8.2.3.4.2
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2376291	2008, IKF-309 Technical: Chronic effects to Daphnia magna, DACO: 9.3.3
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2376294	2013, IKF-309 TECHNICAL: a 96-hour flow-through acute toxicity test with the saltwater mysid (Americamysis bahia), DACO: 9.4.2
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2376297	2007, IKF-309 Technical: Acute Toxicity to Oncorhynchus mykiss (Rainbow trout), DACO: 9.5.2.1
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2376302	2012, IKF-309 Technical: Acute Toxicity to Cyprinus carpio (Common carp), DACO: 9.5.2.2
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2376331	2013, IKF-309 TGAI: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER ALGA (Anabaena flos-aquae), DACO: 9.8.2
2376332	2012, IKF-309 TGAI: a 96-hour toxicity test with the freshwater diatom (Navicula pelliculosa), DACO: 9.8.2
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2376528	2013, Terrestrial Field Dissipation of IKF-309 Applied to Bareground in Kerman, CA - USA 2011, DACO: 8.3.2
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4.0 Value

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2418197	2014, Deficiency Response - Value Pyriofenone, DACO: 10.2.3.3